Introduction

It would have been difficult to find a way in which DISEASES OF THE CHEST could be more highly honored than by the request of Herman Moersch's colleagues to publish an issue dedicated to him. These authors are physicians of great stature among others in the fields they represent throughout the world. Therefore, this issue not only pays tribute to a physician known around the world for his accomplishments but also includes a fine array of papers containing well-documented information by his associates who likewise are known around the world for their accomplishments.

To have been chosen a fellow at the Mayo Foundation was proof positive that every detail of Dr. Moersch's previous life and work had been carefully investigated and he had been found highly desirable.

After he had spent 42 months in general medical and surgical diagnosis and 12 months in neurology, his record was such that he was prevailed upon to accept a first assistantship in a special thoracic section of the Mayo Clinic in 1924 and membership on the permanent staff in 1926. By 1938 he was head of his section, and in 1947 he was promoted to professor of medicine in the Mayo Foundation, a part of the Graduate School of the University of Minnesota.

I first met Herman Moersch when he was a student in anatomy in medical school in 1917. Throughout our 43 years of professional and other pleasant associations I have observed his activities and accomplishments with great pride. As a teacher of graduate students and as a physician he has always been in a superior position. Requests for speaking engagements have come to him from almost everywhere. Editorial boards of medical journals have sought his manuscripts.

At all times, he has recognized good qualities and work of others, and has openly praised the deserving. He has never manifested egotism or selfishness. Indeed, it is these qualities together with superior accomplishments that have resulted in the high regard the medical profession has for him. He has frequently repeated and emphasized that, "No man is big enough to be entirely independent of others."

In an address during the inaugural ceremony of the Fourth International Congress on Diseases of the Chest in Cologne, Germany, in 1956, Doctor Moersch said, "We anticipate that the exchange of information and ideas that we are about to enjoy will not only prove to be a benefit to mankind but also lead to a greater peace which is so necessary to a full and happy life." There, in the presence of many physicians from around the world he accepted with admirable humility the Grand Cross of Merit from the West German Republic.

There is nothing in life that remotely approaches experience. Since 1924 he has worked in a clinic, which is second to none from the standpoint of the number of patients adequately examined and successfully treated.

Dr. Stuart W. Harrington, so long chief thoracic surgeon at the Mayo Clinic, has observed Dr. Moersch and his work throughout his professional career. His beautiful dedication which follows is most sincere, and expresses the feeling a host of physicians have for Herman Moersch.

J. Arthur Myers, M.D., F.C.C.P.

Herman J. Moersch, M.D., F.C.C.P.

DISEASES of the CHEST

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Dedication

This number of DISEASES OF THE CHEST is dedicated to Dr. Herman J. Moersch. The papers it contains have been written by those consultants of the Mayo Clinic who are especially interested in the diagnosis and treatment of thoracic diseases. By their contributions, they express their admiration and esteem, and the warmth of their affection, for Dr. Moersch on the occasion of his retirement from active service in care of patients and in assistance to colleagues, functions that he has skillfully, willingly and graciously fulfilled during the 36 years of his practice and teaching of medicine in Rochester, Minnesota.

I am pleased to have the privilege of adding here my tribute to Dr. Moersch. Compared with some of his present colleagues, I, who shared with him the formative days of his specialty, have had an earlier and longer association with him. Perhaps, then, I more fully appreciate his great contributions, not only to the management of patients with thoracic diseases but also to the development and final organization of a department to care for patients suffering from these conditions.

When I came to the clinic in 1914, there was only one specialized section of medicine and surgery, and that was devoted to orthopedic conditions. At that time, however, Dr. William J. Mayo recognized the advisability of special medical and surgical consideration for patients suffering from thoracic conditions. Dr. Henry Plummer was head of one of the four general medical sections of the clinic at the time. Early in his practice, he became interested in the physiologic aspects and the management of pathologic conditions of the thorax. He published his first paper in 1906, and it was on cardiospasm. His early work in this field was the beginning, in the clinic, of giving special attention to diseases of the thorax. However, a special thoracic section was not established until 1918, when Dr. Willis S. Lemon became head of such a department.

Dr. Herman J. Moersch entered the Mayo Foundation, which is a part of the Graduate School of the University of Minnesota, in 1921, and in 1924 he was appointed to what then was generally called Dr. Lemon's section. In 1937, Dr. Lemon took the lighter duties of senior consultant, and Dr. Moersch was appointed head of the section. Dr. Plummer and Dr. Lemon laid the foundation on which Dr. Moersch and his colleagues have built one of the most efficient sections in the clinic, as well as a thoracic department that I believe to be worthy of the emulation of world medicine.

It was extremely fortunate that Dr. Moersch became head of this special section at a time when great progress was beginning to be made in the field. His outstanding knowledge of thoracic disease and his great

ability to organize and coordinate were most important factors in the development of expertness in diagnosis and treatment of thoracic conditions at the clinic. His accomplishment was attributable not only to his scientific knowledge and skill but notably to his delightful personality, evidenced in his approachability, his thoughtfulness and his generous giving of time and energy to his patients and his colleagues.

Dr. Moersch's patients will regret his retirement and his colleagues will miss his counsel, but his many friends and the fellows of the Mayo Foundation who studied under him wish him happiness and contentment in his retirement. It is fitting to publish a group of papers dedicated to Dr. Moersch as one number of DISEASES OF THE CHEST, the official publication of the American College of Chest Physicians. This prominent medical organization is one in which Dr. Moersch has manifested great interest and of which, in recognition of his contributions, he was made president for 1956-1957. At the time of the Fourth International Congress on Diseases of the Chest, held in Cologne in 1956, Dr. Moersch received the Grand Cross of Merit, the highest decoration that the Government of the Federal Republic of Germany (West Germany) can bestow on a physician.

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Surgical Treatment of Pulsion Diverticula of the Hypopharynx: One-Stage Resection in 478 Cases*

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Diverticula may occur in any part of the esophagus. There are two general types: traction diverticula and pulsion diverticula. Traction diverticula are usually located in the middle third of the esophagus. They occur rather frequently, but usually have a large mouth and empty themselves freely so that they rarely cause symptoms or require treatment of any kind. Pulsion diverticula occur either at the lateral wall of the lower third of the thoracic portion of the esophagus or at the posterior wall of the hypopharynx near the junction of the pharynx and the esophagus. The former are called "epiphrenic" or "supradiaphragmatic" pulsion diverticula of the esophagus. The latter are actually pulsion diverticula of the hypopharynx, but are commonly known as pharyngo-esophageal diverticula. Diverticula most commonly requiring surgical treatment are those arising at the hypopharynx, and the remainder of this presentation will be concerned with these lesions and their management.

A pulsion diverticulum of the hypopharynx is a protrusion or herniation of the mucosa and submucosa of the hypopharynx through a muscular defect in the posterior wall of this structure. Diverticula of this type are remarkably constant in their location, which would indicate that the patient with such a lesion probably has a congenital defect in the muscular wall of the hypopharynx at the point of origin of the diverticulum. Although some rather complicated theories have been advanced to explain the cause and development of these diverticula, the situation actually seems quite clear. The act of swallowing results in pressure against the walls of the hypopharynx and esophagus. At the congenitally deficient or weakened place in the posterior wall, the pressure herniates the mucous and submucous layers through the defect. Gradually over a period of years this herniation develops into a true diverticulum. Once having developed, these pulsion diverticula tend to increase in size at an accelerating rate and to produce symptoms of increasing severity. Although these diverticula appear to have a congenital origin, it should be pointed out that it takes years for them to develop. The average age of patients treated surgically in our experience is approximately 55 years, and the youngest patient on whom one of us (O.T.C.) has operated for this condition was 34 years of age.

Symptoms and Diagnosis

As would be expected, the symptoms produced by pulsion diverticula of the hypopharynx are related to accumulation of food and liquids in the diverticulum and to obstruction to the passage of liquids and food

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into the esophagus. The earliest symptom is a sensation that food seems to catch in the throat when swallowing is attempted. Later regurgitation of undigested food and mucus may occur after eating. Swallowing may be accompanied by a gurgling noise, which may be a source of considerable embarrassment. There may be a sensation of fullness in the throat that can be relieved by pressure applied to the sides of the neck. Once the diverticulum develops it tends to increase in size rather rapidly as it is distended by the pressure involved in the act of swallowing and the more or less constant distention by retained food and secretion. The sac tends to extend downward between the esophagus and the prevertebral fascia into the mediastinum. As the diverticulum increases in size and descends, it tends to angulate the esophagus and obstruct the esophagus both by the angulation and by pressure of the filled sac against the posterior wall of the esophagus. Eating becomes a slow, laborious process, and loss of weight and severe malnutrition can occur. Severe coughing and choking spells may occur due to regurgitation of the contents of the diverticulum into the trachea. Aspiration pneumonitis and lung abscess may be serious complications of a neglected pulsion diverticulum of the hypopharynx.

The presence of a pulsion diverticulum can be strongly suspected from the patient's symptoms. Confirmatory evidence of the diagnosis can be obtained simply by watching the patient drink a cup of water and listening for the gurgling noise that swallowing produces in the presence of a diverticulum. The diagnosis can be firmly established by appropriate roentgenologic examination. Esophagoscopy usually is not necessary in patients with these diverticula. In fact, it should not be performed in most cases because of the danger of esophageal injury. If, because of some unusual clinical or radiologic finding, esophagoscopy should be indicated for a patient with a pulsion diverticulum, it should be performed with particular caution. It is often wise to perform esophageal dilatation before operation for pulsion diverticula of the hypopharynx to relieve any obstruction of the pharynx or esophagus that might have resulted from the diverticulum. This can be accomplished easily and safely if it is performed using a previously swallowed silk thread as a guide for the dilating bougie. A few years ago it was our practice to perform preoperative dilatation routinely. In recent years it has been used only for patients with large diverticula and with severe degrees of angulation and obstruction.

Treatment

Although pulsion diverticula of the hypopharynx were first recognized almost 200 years ago, effective treatment for this condition was slow to develop. Surgical excision was first attempted in the latter part of the nineteenth century. The early operations were associated with high mortality and morbidity rates. In the early years of the twentieth century a two-stage operation was developed and it greatly reduced the complications and hazards of operation for this lesion. As recently as 1954 some experienced surgeons preferred and strongly advocated a two-stage operation for these lesions. There is no question that the two-stage operation is a safe and effective means of dealing with them. How-

ever, this technic does require two surgical procedures, two anesthetics, and a rather long period of hospitalization and convalescence. Surgical technics have been developed that permit a one-stage operation that is at least as safe and effective as the two-stage operation and which requires a much shorter period of hospitalization and postoperative attention.

During a 14-year period, from January 1, 1944, through December 31, 1957, 478 consecutive patients with pulsion diverticula of the hypopharynx were operated on by a one-stage procedure. During this entire period no patient was seen whose lesion was treated by a two-stage operation. The average age of patients operated on was more than 55 years of age. The youngest patient operated on was 28 years of age. Many patients were in the sixth decade of life, and a few were in the seventh decade. Many patients were debilitated and malnourished as a result of their lesion, and some had serious pulmonary complications resulting from their lesion. Four of the 478 patients died in the immediate postoperative period. The surgical mortality rate was 0.8 per cent. Esophagocutaneous fistulas developed postoperatively in four patients. All fistulas closed spontaneously in from 1 to 3 months. Infection of the wound of varying degrees without formation of a fistula developed in five cases. All wounds healed with adequate drainage. There were no instances of serious mediastinal infection. Unilateral paralysis of the vocal cord was noted postoperatively in 11 patients. In eight patients the paralysis was temporary and function was normal within 3 months. In three patients paralysis of the vocal cords was permanent. The average duration of hospitalization for all patients in this series was approximately 8 days. In recent years most patients have left the hospital within 5 days. The average time required from operation to final surgical dismissal for the entire series was approximately 13 days. In recent years this period has averaged 8 days.

A complete follow-up study of all the patients treated by one-stage excision of diverticula in this series has not been attempted. However, follow-up information was available on approximately half of the series. Symptoms or roentgenologic evidence of recurrence of the diverticulum had developed in six patients. Narrowing of the esophagus at the site of resection of the diverticulum requiring postoperative dilatation occurred in three patients. Seven additional patients complained of some dysphagia, although no definite organic cause could be detected. All other patients were completely asymptomatic.

The indications for operation for pulsion diverticula of the hypopharynx are clear. Small diverticula do not produce any symptoms of consequence. A diverticulum that is large enough to produce symptoms sufficient to lead to its diagnosis is large enough to warrant operation for its removal. Since these diverticula tend to increase in size and produce symptoms of increasing severity in spite of any conservative measures that are possible, there are few, if any, contraindications to operation.

Preparation of Patient.—Proper preparation for operation is essential. If there is evidence of marked angulation or obstruction of the esophagus, preoperative dilatation should be performed, with a previously

swallowed silk thread serving as a guide for the dilating bougie. The diverticulum should be emptied of all retained secretions, food, or barium before anesthesia is induced, in order to avoid aspiration of such material into the respiratory tract at the time of operation. If the patient is poorly nourished or dehydrated, appropriate measures should be employed preoperatively to get the patient into the best possible condition. Rarely it may be advisable to perform gastrostomy for feeding purposes. If aspiration pneumonitis or lung abscess has developed as a complication of a diverticulum it should be cleared if possible before proceeding with operation.

Either local or general anesthesia can be used for operation. In our earlier experience cervical block anesthesia was used extensively and was satisfactory. Howver, some nervous, apprehensive patients do not tolerate surgical procedures well under local anesthesia, and in recent years general anesthesia and an intratracheal tube have been used for most patients.

Technic.—Since these pulsion diverticula of the hypopharynx arise in the midline posteriorly, they can be removed equally well from either a right or a left cervical approach. Most diverticula tend to extend slightly to the left, however, and a left cervical incision was used in about 80 per cent of this series.

We have preferred to make the incision along the anterior border of the sternomastoid muscle, extending from the hyoid bone above to a point about an inch above the clavicle. The sternomastoid muscle is retracted laterally and the incision deepened, exposing the omohyoid muscle. The carotid sheath and its contents are retracted laterally; the thyroid gland and larynx are retracted medially, and the pretracheal fascia is exposed. The diverticulum arises from the posterior wall of the hypopharynx at a point a little above the level of the omohyoid muscle. The diverticulum extends downward between the esophagus anteriorly and the prevertebral fascia posteriorly. The diverticulum is grasped with an Allis forceps and elevated into the wound. Dissection is carried down to the neck of the sac and its site of origin. Dissection of the neck of the diverticulum must be performed carefully to avoid injury to the recurrent laryngeal nerve. The dissection must be done thoroughly to avoid leaving a small pouch that might predispose to the development of a recurrent diverticulum.

A variety of technics for excision of the diverticulum and closure and repair of the hypopharynx have been used successfully by the several surgeons who performed the operations reported in this series. The technic used by one of us (O.T.C.) is as follows. After careful dissection of the neck of the sac, a curved clamp is placed over the neck of the sac in a transverse position. The clamp has a pin in its distal end to prevent the diverticulum from slipping out of the clamp. With the clamp on the neck of the diverticulum as a tractor, the mucosa of the hypopharynx is incised in stages proximal to the clamp. Interrupted silk sutures are used to close the mucosa as it is cut; the knots are placed inside the lumen of the esophagus and some of the sutures are left long so that they can be used as tractors. When the diverticulum is completely excised and the mucosa closed, the muscular and fascial layers of the

hypopharynx are closed in a transverse plane with fine continuous catgut sutures.

This technic accomplishes accurate and complete removal of the diverticulum and avoids any danger of narrowing or stricture of the esophagus at the site of repair. A small Penrose rubber drain is placed near the site of repair and the platysma and skin are closed with interrupted sutures. The results of operation by this technic have been unusually satisfactory. It is not necessary to insert a tube through the esophagus for temporary feeding purposes.

The patient is allowed to swallow small quantities of water 24 to 30 hours after operation. The intake of liquid and food is gradually increased. Most patients leave the hospital by the fifth postoperative day and by that time they are able to eat soft foods without difficulty. The Penrose drain is removed on the third postoperative day and the skin sutures on the sixth postoperative day. Patients are advised to chew their food well, to swallow only a small bolus of food at a time, and to omit rough or bulky foods for 2 weeks. The successful results of one-stage operations cannot be attributed to the use of antibiotics, since they were not used routinely in the postoperative management of this series of patients.

SUMMARY

It is apparent from this experience that pulsion diverticula of the hypopharynx occur somewhat commonly. Whenever dysphagia occurs it should be investigated promptly. Diagnosis of diverticula of the hypopharynx can be readily established by appropriate roentgenologic investigation. Surgical excision of diverticula of the hypopharynx can be performed as a one-stage operation with few complications and gratifying results.

RESUMEN

Según esta experiencia los divertículos de la hipofaringe por tracción son algo comunes. Cuando existe disfagia deben ser investigados inmediatamente. El diagnóstico de los divertículos de la hipofaringe puede hacerse facilmente por el examen adecuado a los rayos X.

La excisión quirúrgica de los divertículos de la hipofaringe puede hacerse en un tiempo con pocas complicaciones y con satisfactorios resultados.

RESUMÉ

Il apparait d'après l'expérience des auteurs que l'apparition de diverticules de pulsion de l'hypopharynx est assez banale. Dès qu'apparait la dysphagie, on doit faire très rapidement les investigations nécessaires. Le diagnostic de diverticules de l'hypopharynx peut être rapidement établi par l'investigation radiologique appropriée. Leur exérèse chirurgicale peut être réalisée par une opération en un tempt avec peu de complications et des résultats favorables.

ZUSAMMENFASSUNG

E ergibt sich aus unseren Erfahrungen, dass Pulsations-divertikel des Hypopharyngs ziemlich häufig vorkommen. Wann immer eine Dysphagie auftritt, muss eine sorgfältige Untersuchung vorgenommen werden. Die Diagnose eines Divertikels des Hypopharyngs lässt sich bequem stellen durch eine entsprechende Röntgenuntersuchung. Die chirurgische Excision eines Divertikls ds Hypopharyngs lässt sich als eine einseitige Operation durch führen mit wenigen Komplikationen und erfreulichen Resultaten.

Trauma to the Trachea*

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and JESSE E. EDWARDS, M.D.††

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The trachea may be traumatized in different ways. The purpose of this paper is to call attention to three types of trauma to this organ. The first is that form of trauma caused by a crushing injury to the thorax, the second is that produced by laceration of the trachea and the third is that which may occur after an inflammatory condition, such as diphtheria, which requires tracheotomy.

Traumatic Rupture of the Trachea

Traumatic rupture of the trachea is usually secondary to a crushing injury of the thorax. The rupture may be complete or partial, and it may occur in the cervical or in the thoracic portion of the trachea. The former site is much more vulnerable to injury because of its superficial position. Injuries to the intrathoracic part of the trachea are, fortunately, rare.

It is possible that the state of the glottis at the time of accident is an important factor in rupture of the trachea. If the vocal cords are fixed in the midline, with the patient holding his breath in anticipation of a collision, one would expect the intratracheal and intrabronchial pressure to be greatly increased and that the trachea might rupture when any violent force is transmitted to the thoracic wall.

Persons who have complete tears through all layers of the trachea usually die unless surgical intervention is accomplished early. These tears usually occur on the posterior wall of the trachea, and tension pneumothorax develops rapidly and persists despite all attempts at decompressing the pleural space. Bronchoscopic examination should reveal the laceration; if the tear is found early, thoracotomy is indicated for tears located in the thoracic portion of the trachea.

In partial rupture of the trachea, hemorrhage into the tracheal wall may produce varying degrees of stenosis. Granulation tissue may form readily and also produce tracheal obstruction. Disruption of the attachments of one or more tracheal cartilages usually is present, and this produces tracheal obstruction of varying degrees. The site of rupture is important. It usually occurs in the middle or lower third of the trachea, and thus insertion of the usual tracheotomy tube will not relieve the tracheal stenosis. It is necessary in these instances to use a tracheotomy tube of sufficient length that its distal end passes by the stenotic zone. This will give great relief to the injured patient.

The following four cases illustrate traumatic rupture of the trachea.

Case 1: An acutely ill 29-year-old man came to the Mayo Clinic in April, 1936. Twelve days before, he had been in an automobile accident in which he had struck the steering wheel forcibly over the upper half of the sternum. Following this, he had noted severe pain in this region and had experienced difficulty in breathing.

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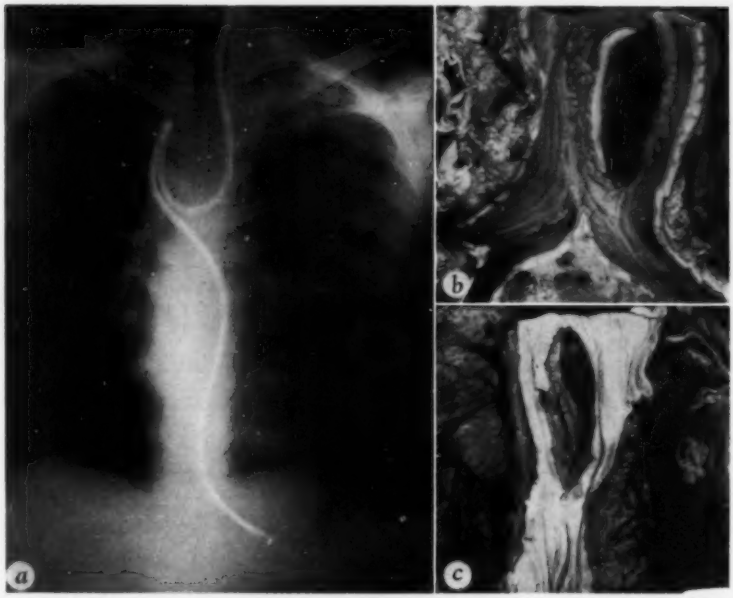

FIGURE 1 (case 1). *a*. Absence of roentgenographic signs of pneumothorax. Note coiled tube in esophagus and superior portion of stomach. *b*. Laceration through posterior wall of distal half of trachea. *c*. Laceration through anterior wall of middle third of esophagus.

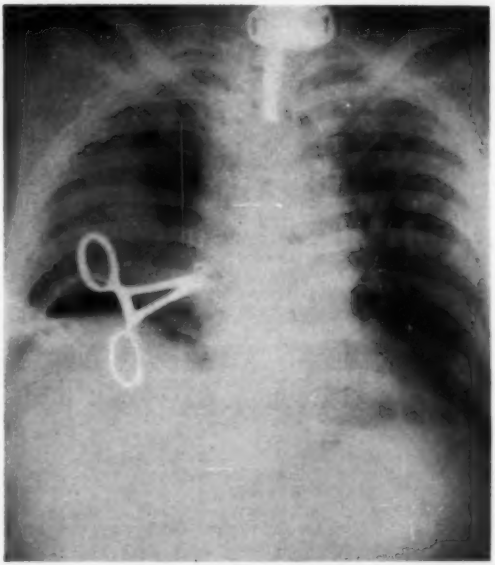

FIGURE 2 (case 2). Roentgenographic appearance prior to admission to the clinic, showing tracheotomy tube in place and towel clip for traction on right anterior thoracic wall. Mediastinal and subcutaneous emphysema was present.

He had coughed up rusty sputum, and his temperature had ranged from 102° to 104° F. up to the time of our examination. Five days after the accident, he had noted difficulty in swallowing. The material that he swallowed would be coughed up almost immediately. Because of this, his home physician had inserted a tube into his stomach for feeding. Three days after his injury, he had started to cough up extremely large amounts of foul-smelling, purulent secretion. He had coughed up about 125 ml. of bright-red blood on one occasion. Roentgenograms taken by his home physician revealed an esophagotracheal fistula.

Roentgenograms of the thorax taken at the clinic revealed a gastric tube in place but did not give any definite evidence of tension pneumothorax (fig. 1*a*). Death occurred 48 hours after admission. Necropsy disclosed a large esophagotracheal fistula caused by traumatic rupture of the trachea and esophagus (fig. 1*b* and *c*).

Case 2: A 53-year-old man was involved in an automobile accident in October, 1956, sustaining a crushed thorax. His home physician performed a tracheotomy and established traction to the right side of the thorax (fig. 2). He noted increasing difficulty in breathing; 6 weeks later, he was extremely cyanotic and dyspneic and was coughing up bloody secretion from the trachea. The tracheotomy had not completely relieved his obstruction, and thus he was referred to the clinic for evaluation 2 months after the accident.

Emergency bronchoscopy at the clinic disclosed severe stenosis of the middle third of the trachea. The trachea was dilated by passing a 6-mm. bronchoscope and finally an 8-mm. bronchoscope beyond the stenotic zone. Biopsy of the stenotic region showed inflammatory granulation tissue. Subsequently, it was thought that the patient had experienced partial rupture of the middle third of the trachea, with hemorrhage into the tracheal wall. It also was believed that one tracheal cartilage had been torn away from its support and that this had caused some of the obstruction.

Insertion of a long tracheotomy tube relieved the patient of all his difficulty in breathing. This tube was left in place for 7 months, after which it was removed, the tracheostoma being kept open by a short tube that did not reach the level of the stenosis. The patient was kept under close observation and underwent bronchoscopic examination on two occasions. Because the stenosis recurred, the long tracheotomy tube again was inserted, and the patient went home for 5 months. At the end of that time, bronchoscopy showed minimal tracheal deformity. The left lateral wall of the trachea bulged in, and slight deformity of the right lateral wall was present; the lumen was adequate. The patient was observed for 5 days, during which the tracheal lumen did not tend to narrow. He was allowed to go home, with the advice to return in 1 month to make certain that the tracheal stenosis had not recurred. A short tracheotomy tube, which did not reach the level of narrowing, was in place.

The patient has continued to do extremely well. The tracheotomy tube was removed in June, 1958, and the opening was closed.

Case 3: A 50-year-old man came to the clinic in March, 1943. Ten months previously, he had sustained a crushing thoracic injury in an automobile accident; 2 or 3 weeks later, he had noted difficulty in breathing. Bronchoscopy in his home community disclosed a "tumor" just above the bifurcation of the trachea. He had undergone bronchoscopy about twice a week since the onset of his respiratory difficulty, with a total of 60 such examinations. After passage of the bronchoscope beyond the obstruction of the trachea, he would get relief for about 4 days and then would have to have the stenosed trachea dilated again.

Examination at the clinic showed that he had stridor at rest. His sternum was depressed as a result of the injury. Bronchoscopy revealed an annular stricture beginning 13 cm. beyond the vocal cords and extending for 4 cm. The distance from the stricture to the carina was 4 cm. The lumen of the trachea was reduced to approximately 4 mm. The stricture was dilated by passing a 7-mm. bronchoscope. Biopsy on four occasions revealed inflammatory tissue. The patient obtained excellent, but only temporary, results from the bronchoscopic dilations. Tracheotomy was done in April, 1943, and a long tracheotomy tube was introduced and passed beyond the level of the stricture. The wall at the stricture was so dense that it was impossible to pass a No. 7 tube, so a No. 6 tube was put in place, which relieved his dyspnea. Bronchoscopy again was done in July, 1943, and it was decided to leave the tracheotomy tube in for a longer period. Bronchoscopy in January, 1944, showed that the tracheal lumen was adequate. The tracheostoma was closed in February, 1944.

The patient wrote in January, 1954, that he was doing very well. His wife later informed us that the patient died of a malignant tumor in May, 1958. The primary source of this lesion was unknown. The patient's wife stated that he had not experienced any difficulty in breathing.

Case 4: A 26-year-old man had been in an automobile accident in June, 1952, and had struck his neck and jaw forcibly on the steering wheel. The left eye also was injured, resulting in blindness of this eye. In addition, he had sustained fractures of the ribs, and the right femur, heel and ankle. Seven hours after the accident, it had been necessary to perform a tracheotomy. Four months prior to our examination, a skin graft of the trachea had been done and an obturator inserted. The obturator had been removed 3 weeks before we saw him.

He came to the clinic in March, 1953 (fig. 3). Suspension and examination of the larynx revealed cicatricial webbing of the subglottic region that completely obstructed the lumen of the glottis and upper part of the trachea. The vocal cords appeared

to be free and normal. Thyrotomy and skin grafting for the subglottic and tracheal stricture were done on March 25, 1953. A large mass of tissue was present just above the tracheostoma in the region of the cricoid cartilage. On cutting into this tissue, an opening into the esophagus was established inadvertently; consequently, the mass of tissue could not be removed. An attempt was made to close this perforation, and a skin graft was wrapped around a sponge-rubber obturator and inserted. The surgeon did not believe that this would provide a permanent lumen through the larynx, because the posterior part of the cricoid cartilage was completely gone. A full-thickness skin graft was taken from the abdominal wall.

On April 1, the rubber obturator was changed. A small hole in the esophagus was still present. On April 3, a wax pattern for a vernonite obturator was made; 3 days later, the vernonite obturator was inserted through the tracheostoma. On May 29, a plastic operation was done on the tracheo-esophageal fistula. A small flap of mucous membrane was elevated just to the right of the fistula. This was "delayed" by suturing it back in its original bed. On June 10, a small flap of mucous membrane to the right of the tracheo-esophageal fistula was elevated, rotated over the fistulous opening and sutured in place. On June 22, a double-pedicle skin flap was elevated along the left clavicle and tubed. It was planned to use the lateral end of this to cover the tracheo-esophageal fistula. On August 5, the distal end of the tube flap was severed through half of its circumference and resutured. On August 24, the lateral end of the clavicular tube flap was cut across so that it could be transferred to the laryngeal region. All of the mucous-membrane lining on the posterior and lateral walls of the trachea around the tracheo-esophageal fistula was excised. This denuded area and the fistula were covered with the lateral end of the tube flap, which was sutured in place with catgut sutures. On September 16, the tube flap was cut across just beyond its attachment at the trachea. The tube flap was saved so that the other end could be used to cover the external tracheal opening. The cut edge of the reconstructed edge of the trachea was sutured back in place. On September 28, an acrylic obturator was made for the stricture in the lower part of the larynx. On January 25, 1954, a wax pattern was prepared for the acrylic obturator to be placed into the laryngeal lumen. On January 29, the obturator was fitted to a new, nonadjustable, No. 8 tracheotomy tube. The remaining part of the clavicular flap on the left side was opened up and was sutured in place to cover the scarred area.

The appliance attached to the tracheotomy tube worked extremely well, enabling the patient to expel air through his larynx and talk satisfactorily. When we last heard from the patient, in August, 1955, he stated that he was "doing fine."

Laceration of the Trachea

Laceration of the trachea can produce stenosis. The following two cases are examples of this type of trauma.

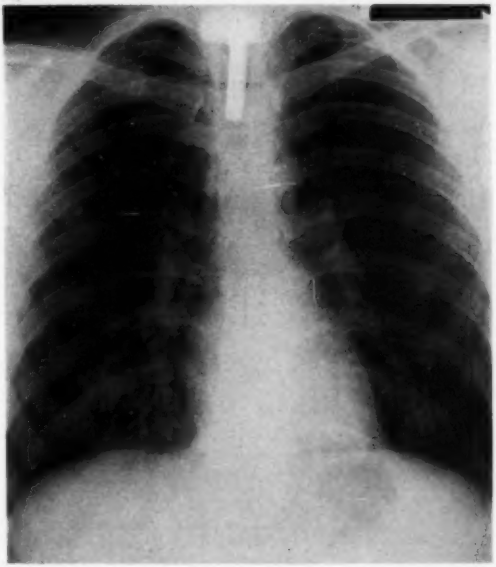

FIGURE 3 (case 4). Roentgenographic appearance at time of admission to the clinic.

Case 5: A 16-year-old boy came to the clinic in February, 1950. Seven months previously, he had sustained a subglottic severance of the trachea in an automobile accident. Primary anastomosis of the trachea had been done, with insertion of a tracheotomy tube for 10 days. During the 4 months prior to admission here, the patient had noted progressive difficulty in breathing and exertional dyspnea and had found that his voice was weak. Climbing three flights of stairs made him short of breath.

Examination at the clinic revealed two scars, one over the cervical portion of the trachea, at the site of the previous operation, and one on the anterior thoracic wall over the sternum. The left vocal cord was paralyzed, but an adequate airway was present at the level of the glottis. Roentgenograms of the trachea taken in the lateral position showed narrowing of the trachea. Bronchoscopy disclosed a circular band of extremely hard scar tissue located 3 cm. below the vocal cords on the anterior and lateral walls; it had reduced the lumen of the trachea to two thirds its normal diameter. This band was cut in two places with scissors inserted through the bronchoscope. Biopsy revealed inflammatory tissue. After this procedure, it was estimated that the lumen of the trachea was restored to 90 per cent of its normal size. The next day, the patient was able to breathe much more easily.

On recheck of his condition 5 months later, he stated he was breathing well but would notice difficulty in breathing if he ran 100 yards. His left vocal cord was still paralyzed. Bronchoscopy showed an adequate lumen. Some scar tissue still was present on the anterior wall of the trachea; this again was cut in three or four places, using scissors inserted through the bronchoscope. Following this procedure, a 9.5-mm. bronchoscope was passed to dilate the trachea further, after which he could breathe much better. Roentgenograms showed that the lumen of the trachea was adequate (fig. 4).

He returned again for examination in January, 1951. At that time, he said that he could run up two or three flights of stairs without trouble.

Case 6: A 6-year-old boy came to the clinic in June, 1935. His insane mother had cut his throat with a knife 14 months previously, cutting across the trachea at a point 4 cm. below the glottis. He was treated by dilation of the trachea with a bougie, and a plastic operation was done on the trachea. Good functional results were obtained despite some degree of stenosis evident roentgenologically 20 years later (fig. 5).

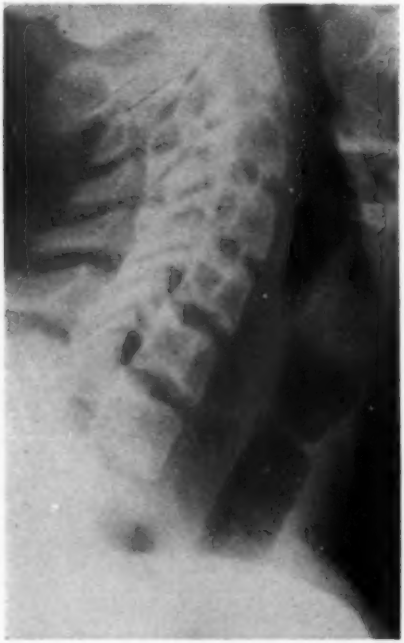

FIGURE 4 (case 5). Lateral roentgenogram taken in July, 1950, showing stricture in cervical portion of trachea.

Inflammatory Conditions Requiring Tracheotomy

Stenosis of the trachea may develop after a severe infection of the respiratory tract that requires tracheotomy. The following cases are examples of this.

Case 7: A 65-year-old woman came to the clinic in February, 1954. At the age of 4 years, she had had a tracheotomy for "croup." The tracheotomy tube had been removed after the acute emergency, but she had noticed mild wheezing ever since. Three months prior to admission, she had had an acute infection of the respiratory tract, and her difficulty in breathing had increased since that time.

Examination at the clinic disclosed an audible wheeze at rest. Roentgenologic examination of the thorax showed narrowing of the trachea above the level of the clavicles, which also was noted on tomograms (fig. 6). Bronchoscopy revealed severe tracheal construction 2 to 3 cm. below the vocal cords and resulting from the tracheotomy scar. Biopsy revealed an inflammatory mucosa with squamous metaplasia. A 7-mm. bronchoscope was used to dilate the stricture.

Case 8: A 55-year-old man came to the clinic in March, 1955. At the age of 7 months, he had had diphtheria, which was followed by respiratory obstruction that necessitated an emergency tracheotomy. After recovery from the diphtheria, the tracheotomy tube was removed. Following this, 56 intubations were necessary. The patient then remained well up to the age of 18 years, at which time the larynx and upper part of the trachea had to be dilated so that he could pass the entrance examination for the U. S. Naval Academy. He then had no trouble until 1947, when it was necessary for him to have six or seven dilations of a subglottic stricture. In August, 1954, after dilation of the larynx and upper portion of the trachea, severe respiratory obstruction developed that necessitated tracheotomy.

Examination at the clinic in 1955 revealed a tracheotomy tube in place (fig. 7). Concentric stenosis was present 1 cm. below the glottis. The airway was narrowed to 7 mm. The patient became dyspneic with slight exertion whenever the tracheotomy tube was corked. On March 28, 1955, a laryngeal fissure was made for cicatricial stenosis of the larynx and upper part of the trachea. It was necessary to divide the cricoid as well as the thyroid cartilage, as the stenosis was most pronounced at the level of the cricoid. Multiple incisions were made through the scarred zone, and a portion of it was excised. An area of benign thickening on the anterior portion of the left vocal cord was excised. A medium-thickness skin graft was taken from a hair-free

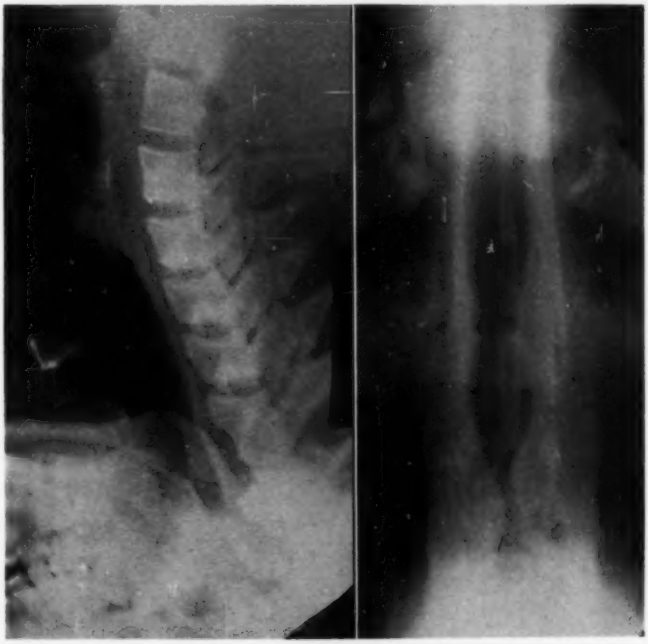

FIGURE 5 (case 6). Anteroposterior and lateral roentgenograms, revealing stenosis of trachea 20 years after injury.

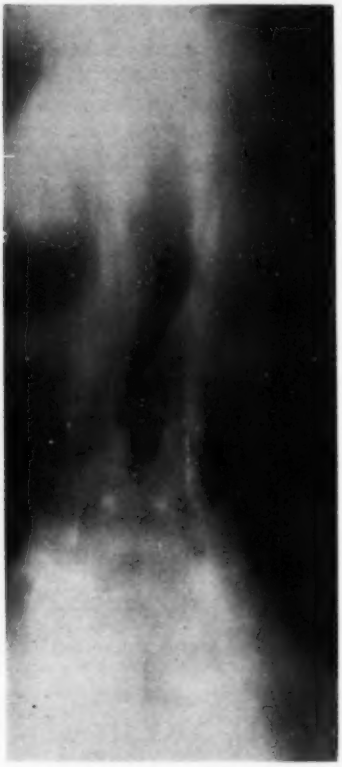

FIGURE 6 (case 7). Tomographic appearance, showing narrowing of cervical part of trachea.

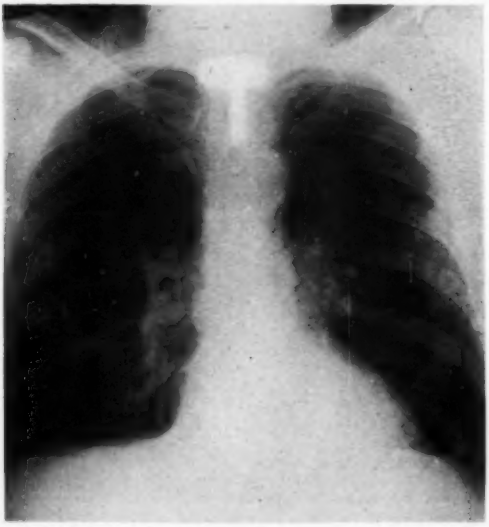

FIGURE 7 (case 8). Roentgenographic appearance on admission to the clinic.

area on the left lateral thoracic wall. This was wrapped about a sponge-rubber mold and inverted to line the denuded portion of the larynx and upper part of the trachea. The stent was removed on April 6. On April 25, suspension and examination revealed a widely open airway. By May 7, the patient was breathing freely after removal of the tracheotomy tube.

In November, 1956, which was 20 months after the last operation, he was seen at another medical center. He could not speak above a whisper. He was told that he had emphysema and that he had lost 60 per cent of his lung capacity.

Case 9: A 51-year-old man came to the clinic in November, 1955. At the age of 5 years, he had had diphtheria, which required tracheotomy. He used a tracheotomy tube most of the time until the age of 10 years, when the tracheostoma was closed. Since then, he had experienced mild exertional dyspnea, noticed most when he tried to engage in sports. Exertional dyspnea had increased slowly but gradually during the 5 years prior to admission.

Examination disclosed inspiratory stridor. Mirror examination revealed cicatricial stenosis of the trachea 2 cm. below the vocal cords. The diameter of the airway was reduced by half. Tomography in 1955 and again in 1957 showed some stenosis of the trachea below the larynx.

When the patient returned for recheck in November, 1957, he thought his dyspnea was increasing. He noticed this while he was doing morning calisthenics, but he had no difficulty during ordinary activities. Studies of pulmonary function showed a maximal breathing capacity of 85 liters per minute as contrasted to an estimated normal of 105 liters. The maximal midexpiratory flow was a low normal of 2.2 liters per second, the average for his age being 3.7 liters. Ventilation during exercise was adequate.

In March, 1959, he wrote that his breathing was possibly not quite so good as it had been. He could not swim as far or shovel as much snow as he had been able to do 5 or 10 years previously. He stated: "I think I puff more and it is hard for me to get air."

COMMENT AND CONCLUSIONS

Tracheal stenosis caused by rupture of the lower portion of the trachea usually can be dilated adequately by employing a tracheotomy tube long enough to pass the level of the stenosis and leaving it in place for approximately a year. Tracheal stenosis in the upper part of the trachea also can be treated by allowing a dilating instrument to remain in place for varying periods. It is necessary at times to do plastic operations in order to secure an adequate airway. If a tracheal stricture can be treated by dilation, it appears that this method of treatment is far superior to resection of the strictured portion of the trachea.

RESUMEN

La estenosis traqueal causada por la ruptura de la porción baja de la tráquea, generalmente puede ser dilatada empleando un tubo de traqueotomía suficientemente largo para pasar el nivel de la estenosis y dejándolo en el lugar aproximadamente por un año.

La estenosis traqueal de la parte superior también puede tratarse al permitir que un instrumento dilatador permanezca en el lugar por períodos variables. A veces es necesario realizar operaciones plásticas para asegurar un paso de aire adecuado. Si la estenosis puede tratarse por dilatación, parece que este método es con mucho superior a la resección de la porción estenosada.

RESUMÉ

Une sténose trachéale causée par la rupture de la partie inférieure de la trachée peut généralement être dilatée d'une façon utile en utilisant un tube de trachéotomie suffisamment long pour passer le niveau de la sténose trachéale de la partie supérieure de la trachée peut aussi être traitée en permettant à un instrument dilatateur de rester en place pendant des périodes variées. Il est nécessaire de temps en temps de faire des opérations réparatrices pour ménager un conduit aérien convenable. Quand la striction trachéale peut être traitée par dilatation il semble que cette méthode de traitement soit de loin supérieure à la résection de la portion sténosée de la trachée.

ZUSAMMENFASSUNG

Eine durch eine Ruptur des unteren Luftröhrenabschnittes entstandene Trachealstenose kahhn für gewöhnlich ausreichend gedehnt werden durch Verwendung eines Tracheotomie-Tubus, der so lang ist, dass tiefer reicht, als die Stenose sitzt, and der für etwa ein Jahr an Ort und Stelle belassen wird. Die Trachealstenose im Bereich des oberen Luftröhrenabschnittes lässt sich gleichfalls so behandeln, dass für ein dilatotorisches Instrument die Möglichkeit geschaffen wird, verschieden lange Zeit an Ort und Stelle zu verbleiben. Gelegentlich ist es erforderlich plastische Eingriffe vorzunehmen, um einen ausreichenden Luftweg zu gewährleisten. Vermag man eine tracheale Striktur durch Dilatation zu behandeln, so ist diese Methode der Resektion des strikturierten Trachealabschnittes allem Anschein nach weit überlegen.

Etiology of Broncholithiasis*

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Broncholithiasis presents many interesting problems relative to diagnosis and treatment. These have been clearly reviewed by Moersch and Schmidt[1] who also emphasized the paucity of information concerning the nature of the causative agents. Since, on the basis of histopathologic evidence, calcified granulomas of the pulmonary parenchyma have until recent years been considered as most likely the result of infection with tubercle bacilli, the inference has been that broncholiths originating in lymph nodes adjacent to the bronchial tree had the same etiologic basis. However, we have not been able to find any reference to direct bacteriologic confirmation of such an etiologic factor in stones. The present study was undertaken therefore with the view of obtaining information concerning the nature of any organisms that might be present in broncholiths.

Material, Method and Results

The broncholiths used were obtained from patients currently under observation (six cases) and from stored specimens obtained from patients previously studied (three cases). The stones were examined by dividing them into two parts, one to be decalcified and studied by special staining of the histologic sections, and the other to be pulverized to a fine paste in a sterile mortar and suspended in broth for culture for Brucella, fungi, acid-fast bacilli and common pyrogens (aerobes and anaerobes) including Hemophilus. The technics for staining the histologic sections included the silver chromate technic for fungi,[2] the night blue technic for acid-fast bacilli[3] and the Brown-Breen technic for the gram stain and the routine hematoxylin and eosin stain.

The results are summarized in the table and illustrated in figures 1 to 4.

Comment

With each of the special staining technics, the structures observed are presumed to be organisms; this we believe to be justified in view of our experiences with these stains when used in conjunction with other clinical and surgical specimens from which the organisms are isolated and identified. The special stains alone cannot be used to positively identify the organisms as Histoplasma or Nocardia, although such designations are compatible with the evidence.

The value of the silver chromate technic for staining fungi has been adequately demonstrated by Grocott[2]. However, as emphasized by Segal and associates[4], this technic will permit one to determine only size and shape of the organism and is not specific for any particular species. Since many of the fungi vary in size and shape as seen in histologic section[5], the technic does not permit precise identification of the type of yeastlike organism being observed. Further studies with specific fluorescent antibody technics may make it possible to identify the organisms, but these studies are not yet completed. However, the silver chromate technic is very important as a method of demonstrating structures that are not visible with the hematoxylin and eosin, night blue or Brown-Breen gram technics.

The night blue stain as described by Hallberg[3] has been modified by using safranin (0.01 per cent) as a counter stain to give a strong contrast with the blue and to faintly

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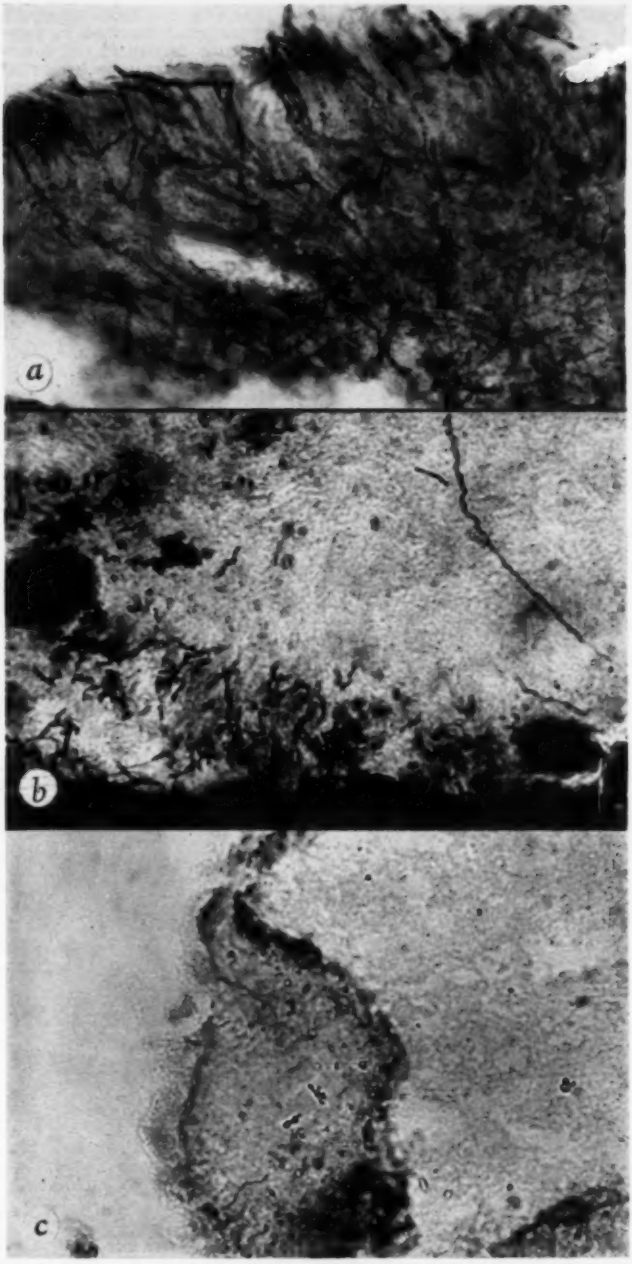

FIGURE 1 (case 1): Broncholith containing only filaments demonstrable by special stains. *a*. Numerous granular tangled filaments (silver chromate; x1100). *b*. Tendency to form bacillary and coccoid forms suggestive of some species of Nocardia (gram stain; x1100). *c*. Two acid-fast filaments but numerous coccoid forms further suggestive of a species of Nocardia (night blue; x1100).

outline the tissue and inflammatory cells so that one can have perspective of the topography of the lesion. The organisms in the broncholiths that we have observed by this technic are much too long and filamentous to be considered tubercle bacilli. The acid-fast property of some strains of Nocardia (table) makes one suspect that this might be the true nature of the organisms observed. The Brown-Breen technic is very useful for demonstrating in tissue sections the fine filaments of Nocardia when this organism is isolated by culture from a surgical specimen. Nocardia stains by the gram and the silver chromate technics, and the strains that are acid fast also stain with night blue. Therefore, one has much more evidence on which to suspect Nocardia than Histoplasma, since the latter is not uniformly stained, except perhaps with silver chromate. The staphylococci, which are easily visible with the gram stain, occur only as cocci and in clusters, and are therefore easily differentiated from the coccoid forms of Nocardia since the latter also have bacillary and filamentous forms.

It is not surprising to find forms suggestive of Histoplasma in a broncholith, since calcification occurs frequently in intrapulmonary histoplasmosis and this infection

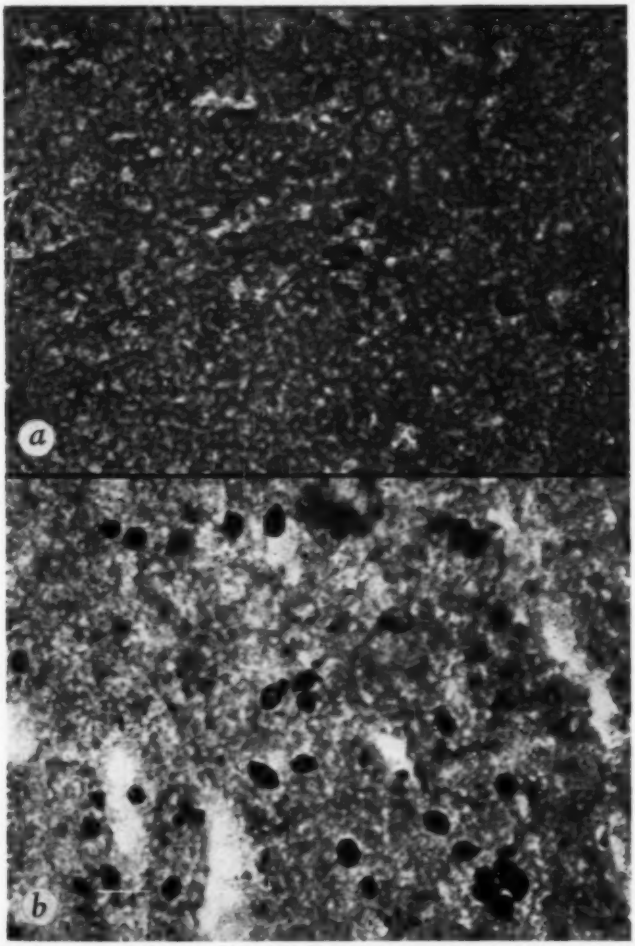

FIGURE 2 (case 2): Broncholith containing only oval bodies demonstrable by silver chromate method of staining. *a*. Broncholith stained with hematoxylin and eosin to show the finely granular matrix and the absence of organisms visible by this commonly used procedure. *b*. Broncholith stained by silver chromate technic to show oval bodies 3 to 5 microns in diameter whose appearance is compatible with that of Histoplasma.

also is likely to involve the hilar lymph nodes. In view of the report by Segal and associates[4], it is also not surprising to find that cultures of such lesions are negative for Histoplasma although silver chromate stains show structures that have the morphologic features of this organism. The broncholiths examined were from patients who have lived mainly in areas where histoplasmosis is common.

Coccidioides, which stimulates the production of lesions closely similar to those of histoplasmosis, might also be expected to be found in broncholiths obtained from patients residing in areas where this organism is prevalent. It would be a surprise, however, to find Blastomyces in a broncholith, since intrapulmonary lesions due to this organism apparently do not commonly calcify and, in our experience, usually do not invade the lymph nodes.

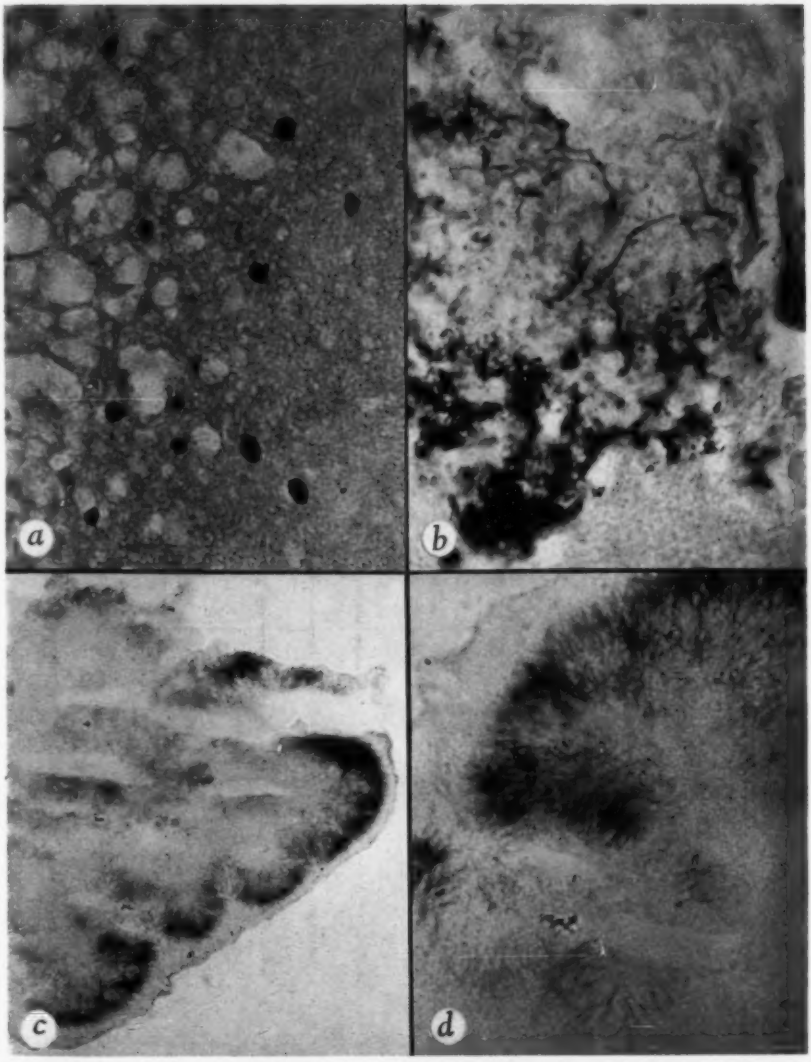

FIGURE 3 (case 8): Broncholith containing both oval bodies and filaments demonstrable by the various methods of staining. *a*. Oval bodies 3 to 5 microns in diameter as stained by the silver chromate technic (x1100). *b*. Fine branching filaments and coccoid bodies as stained by the gram technic (x1100). *c*. Numerous radially placed filaments stained by the night blue technic (x400). *d*. Same as *c* (x1100).

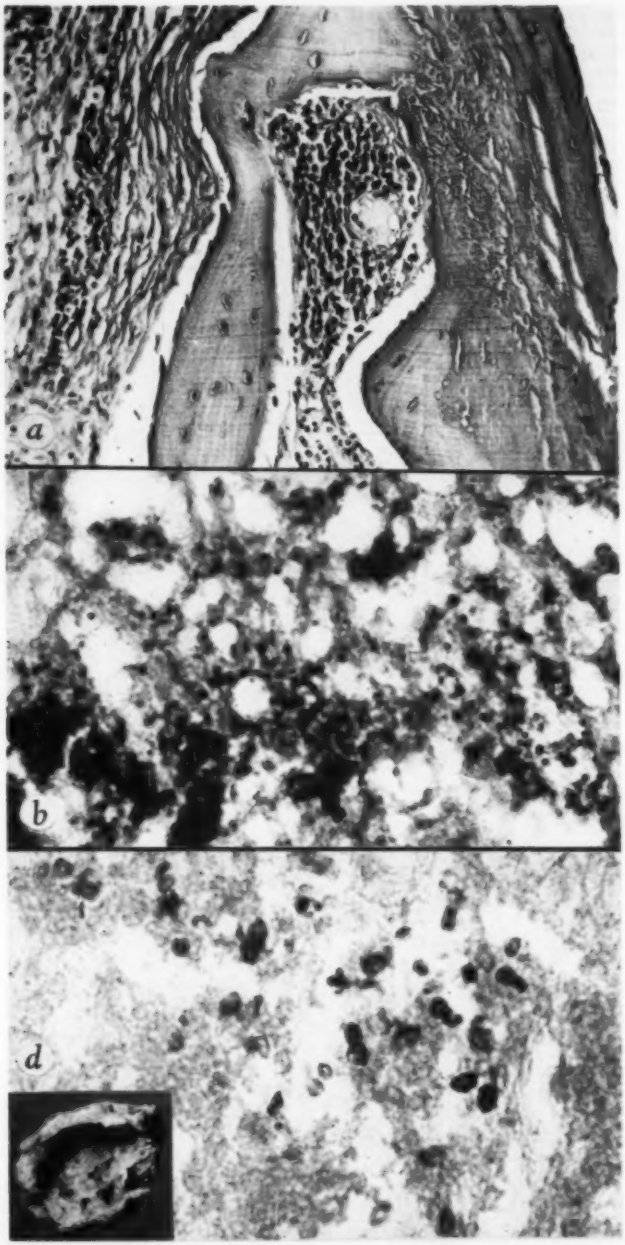

FIGURE 4 (case 9): Broncholith showing bone formation and surface contamination with staphylococci. *a*. Specimen stained with hematoxylin and eosin to illustrate bone formation (x185). *b*. Numerous spherical organisms 1 micron in diameter appearing singly and in masses on the surface of the broncholith. Cultures positive for Staphylococcus aureus (gram stain; x1100). *c*. Numerous oval bodies stained with silver chromate (x1100). *Inset*. Gross specimen showing sharp-pointed corners and irregular surfaces.

TABLE — DATA ON BRONCHOLITHS STUDIED BACTERIOLOGICALLY

Case	Specimen	Culture	Stain: Night blue	Stain: Gram	Stain: Silver chromate	Age, sex	Occupation	Symptoms, duration	Residence	X-ray findings
1	A	Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	36 M	Shop foreman, oil company	Ac. pneumonia 9 mo. previously, cough since	North Dakota	Calcified hilar masses, fibrosis beyond these. Bronchoscopic removal
	B	Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia					
2		Neg.	Neg.	Neg.	+Oval bodies, 3-5 microns. ?Histoplasma	47 F	Housewife	2 years	Born Brazil, to U.S. age 1. Illinois	Infiltration R.M.L., calcified R. hilar nodes
3	A	Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	54 M	Farmer	3 years	Born Ohio. New Mexico	Bilateral broncholiths, calcified hilar nodes
	B	Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia					
	C	Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia					
4		Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	Few oval bodies, 3-5 microns. ?Histoplasma	66 F	Housewife	4 years	Born Iowa. Montana	Calcified hilar node, stones expectorated
5		Staph. aureus	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	17 M	Student	5 years	Indiana	Calcification R. hilus and R. paratracheal region. Contracted R.M.L. Broncholith found by bronchoscopy
6		Neg.	No filaments Few coccoid forms	+Fine filaments ?Nocardia	+Many fine filaments ?Nocardia Very few oval bodies, 3-5 microns. ?Histoplasma	73 M	Farmer	10 months, cough and loss of weight	Indiana	Pneumonitis L.L. lobe. ?Bronchiectasis or obstruction L.L.L. bronchus
7		Neg.	Neg.	Neg.	Oval bodies, 3-5 microns. ?Histoplasma					
8		Neg.	+Fine filaments ?Nocardia	+Fine filaments ?Nocardia	Oval bodies, 3-5 microns. ?Histoplasma	59 F	Housewife	4 years, cough, wheezing. Pneumonia	Illinois	Calcified hilar node. Nodular process L. costophrenic region
9		Staph. aureus	Neg.	Bone formation. Masses of staphylococci	Many oval bodies, 3-5 microns. ?Histoplasma	55 F	Unknown	6 months	Illinois	Calcified R. hilar node

Cryptococci, however, while not as frequent a cause of intrapulmonary lesions as Histoplasma or Coccidioides, usually do invade lymph nodes, do at times stimulate the deposition of calcium, and might easily be confused morphologically with the endospores of Coccidioides (but not the spherules) or with Histoplasma. One would not expect the special stains for capsules as seen in early lesions in soft tissues to give reliable information when applied to a broncholith.

Histoplasma capsulatum is suspected of being present, as given in the table, on the basis of the presence of oval or spherical forms 5 to 7 μ in diameter, uniform in size, and demonstrable only with the silver chromate technic. Their identity, in the absence of positive results on culture, would depend on their reaction with specific antiserum using the fluorescent technic. This is being studied at present, but the difficulty of producing antisera for fungi that will be both specific and sensitive is well known. While Pneumocystis carinii also takes the silver chromate stain[6] and has about the same size and shape as Histoplasma capsulatum (but not H. duboisii), we know of no evidence that it produces chronic localized lesions or local areas of calcification.

Intrapulmonary nocardiosis is primarily a suppurative disease[7] with little or no tendency to the deposition of calcium. If the broncholith originates from infection involving the parabronchial lymph nodes with Nocardia, the pathogenesis of calcification must be quite different from that found in caseous granulomas due to Histoplasma. The mechanism of calcification in any case is poorly understood and constitutes a separate problem. Nevertheless, if the filaments observed are really Nocardia, it is interesting to speculate why they are found so commonly in such infrequently encountered lesions as broncholiths when intrapulmonary nocardiosis also is not common.

SUMMARY

By use of known reliable cultural technics and by special stains of histologic material, we have examined 12 broncholiths obtained from nine patients. By means of the silver chromate technic, we have been able to demonstrate bodies that have the morphologic features of Histoplasma capsulatum in five stones from five patients. By means of the gram and night blue stains we have been able to demonstrate branching filaments whose morphologic appearance is compatible with that of Nocardia asteroides in eight stones from five patients. In two stones (two patients), structures resembling both Histoplasma and Nocardia were present in generous numbers. Staphylococci were found in large numbers by culture in two stones. By means of the gram stain, they were shown to be only on the surface and were presumed to be contaminants and not the original stimulus to the deposition of calcium.

RESUMEN

Hemos examinado 12 bronquiolitos obtenidos de nueve enfermos mediante el uso de técnicas de cultivo así como por coloración especial del material histológico.

Por medio de la técnica del cromato de plata, hemos podido demostrar cuerpos que tienen las características morfológicas del histoplasma capsulátum en cinco piedras de cinco enfermos.

Por los colorantes de Gram y los azules intensos hemos podido demostrar ramas filamentosas cuya morfología es semejante a la nocardia asteroides en ocho piedras de cinco enfermos. En dos piedras (dos enfermos) se encontraron estructures parecidas tanto al histoplasma como a la nocardia en gran cantidad.

Se encontraron estafilococos en gran número por cultivo de dos piedras. Por el Gram se encontraron sólo en la superficie por lo que se presume que fueron contaminaciones y no estímulos originales para la concreción de calcio.

RESUMÉ

En utilisant des techniques de cultures connues et valables, et au moyen de colorants spéciaux du matériel histologique, les auteurs ont examiné 12 bronchiolithes obtenus sur 9 malades. Au moyen de la technique au chromate d'argent, ils ont été capables de mettre en évidence des corps qui ont les caractéristiques morphologiques de l'histoplasma capsulatum dans cinq calculs provenant de cinq malades. Au moyen des colorations de Gram et de bleu ils ont pu mettre en évidence des filaments ramifiés dont l'apparence morphologique peut être attribuée à Nocardie asteroïde dans huit calculs provenant de 5 malades. Dans deux calculs (provenant de 2 malades) des aspects ressemblant à la fois à l'histoplasma et au nocardia se rencontraient en grand nombre. Dans deux calculs des staphylocoques furent trouvés en abondance à la culture. Au moyen de la coloration de Gram, les auteurs montrèrent qu'ils ne siégeaient qu'à la surface et on put les considérer comme des agents d'infection secondaire et non comme la cause primitive de la formation des calculs.

ZUSAMMENFASSUNG

Unter Verwendung von bekannten zuverlässigen Methoden der kulturellen Züchtung und mit speziellen Färbungen von histologischem Material untersuchten wir 12 Bronchialsteine, die von 9 Kranken stammten. Unter Zuhilfenahme der Silberchromattechnik war es uns möglich, Bestandteile nachzuweisen mit den morphologischen Merkmalen von Histoplasma capsulatum in 5 Steinen von 5 Kranken. Mit Hilfe der

Gramund Nachtblau-Färbung gelang es uns, sich verzweigende Filamente nachzuweisen, deren morphologisches Aussehen vergleichbar ist Nocardia asteroides und zwar in 8 Steinen von 5 Kranken. In 2 Steinen von 2 Kranken lagen in grosser Zahl Strukturen vor, die sowohl Histoplasma als auch Nocardia ähnelten. In 2 Steinen fanden wir aufkulturellem Wege in grosser Zahl Staphylokokken. Mittels der Gram-Färbung liess sich nachweisen, dass sie ausschliesslich an der Oberfläche lagen, weshalb angenommen werden kann, dass es sich um Verunreinigungen handelt und nicht um den ursprünglichen Reiz zur Kalkabscheidung.

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"Occult" Carcinoma of the Bronchus: A Study of 15 Cases of In Situ or Early Invasive Bronchogenic Carcinoma*

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The importance of duration of an in situ stage in the evolution of bronchogenic carcinoma has yet to be determined. Black and Ackerman[1] and Carlisle and associates[2] have reported that carcinoma in situ frequently surrounds an invasive bronchogenic carcinoma. In a study of necropsy specimens Ryan and co-workers[3] found carcinoma in situ in the opposite lung in 12 per cent of the cases in which resection had been performed for bronchogenic carcinoma. Auerbach and co-workers[4] used serial block section and found carcinoma in situ (or atypical metaplasia) in the bronchi of 75 per cent of heavy smokers and an equally high incidence in patients known to have bronchogenic carcinoma.

Pulmonary resection for carcinoma in situ of the bronchus has seldom been reported.[5,6] Theoretically such early lesions should not show evidence of abnormality on thoracic roentgenograms unless some degree of associated obstructive pneumonitis is present and, in the absence of a tumor, they should not be detected readily on bronchoscopic examination.[7] Although exfoliative cytology has proved to be valuable in the diagnosis of bronchogenic carcinoma in cases with suspicious symptoms or roentgenologic findings,[8] its usefulness as a screening device in roentgenologically asymptomatic patients has not yet been determined. It has been postulated that such screening, perhaps with the aid of aerosol technics, might result in the detection of bronchogenic carcinoma at an earlier stage or even in the in situ or intramucosal phase of its development.

A review of apparently early cases of resected bronchogenic carcinomas was undertaken to determine the incidence of positive cytologic findings and the means by which the diagnosis was established. Follow-up data were obtained to determine the prognosis after resection of these early lesions.

Materials and Methods

A survey of pathologic reports on resected bronchogenic carcinomas over a 13-year period, 1946 to 1958 inclusive, at the Mayo Clinic revealed a number of cases in which the lesion was occult in that no tumor was visible on gross examination of the specimen. In many of these cases the carcinoma proved to be predominantly or entirely in situ. Many sections were obtained from all such lesions by means of the serial block technic to determine the extent of the in situ change and the depth of associated infiltration if such was present.

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The study included five cases in which lesions had been reported previously as predominantly in situ carcinomas.[4] These were re-examined by serial block technic to determine whether areas of infiltration could be found on more complete sampling. An absolute or exact line between in situ and infiltrative carcinoma of the bronchus proved somewhat difficult to establish in that involvement of ducts of mucosal glands cut tangentially may at times be difficult to distinguish from early superficial infiltration.

After excluding all cases with infiltration beyond the bronchial wall, a total of 15 bronchogenic carcinomas in the early stages of development were selected for study. These were divided into three groups as

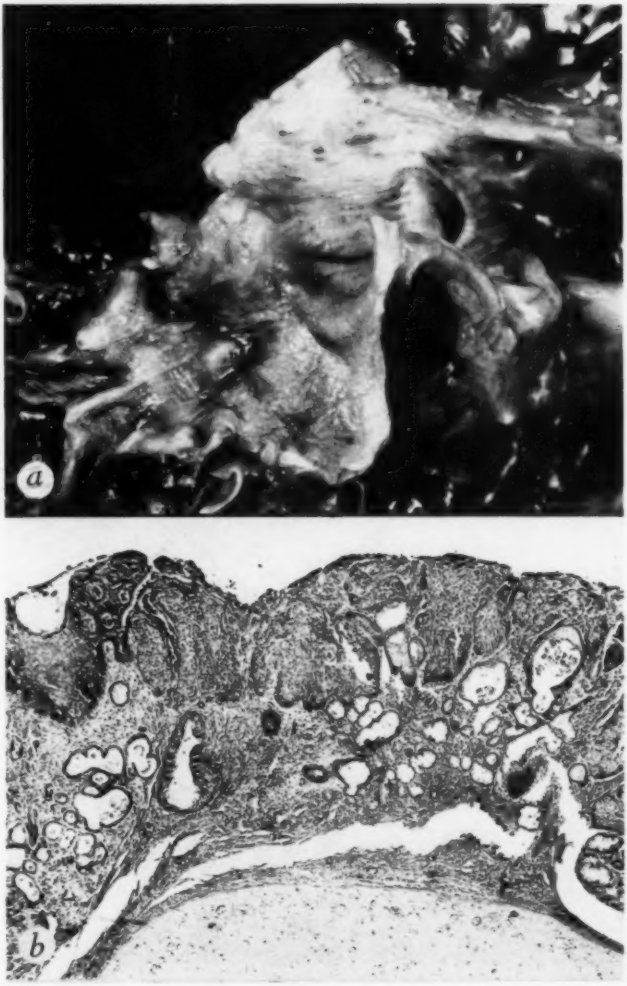

FIGURE 1 (case 3): *a*. Gross appearance of resected lung showing extensive in situ carcinoma of right main and upper lobe bronchus. *b*. Histologic section through lesion showing in situ change in surface mucosa with little or no infiltration (hematoxylin and eosin; x35).

TABLE 1 — IN SITU BRONCHOGENIC CARCINOMA WITH NO OR EQUIVOCAL EVIDENCE OF INFILTRATION

Case	Sex, age yr.	Symptoms	Duration	X-ray of thorax	Result of bronchoscopic examination	Result of cytologic examination	Operation	Pathologic findings	Last report
1	M 55	Dry cough	2 mo.	Emphysema; apical segment, left upper lobe lung	Negative	Sputum: positive (squamous cell cancer); bronchial secretions, left upper lobe: positive	Lobectomy, left upper lobe (no tumor palpable)	Squamous cell carcinoma in situ, grade 3, with equivocal superficial infiltration involving 1.2 cm. of the apical segment of left upper lobe branch	No report, recent case
2	M 63	Severe cold with fever 7 mo. prior to admission; one episode hemoptysis; cough	3 wk.	Poorly defined infiltration in left upper lobe	Negative	Sputum and bronchial secretions from left upper lobe: positive for cancer cells	Pneumonectomy, left lung	Moderate obstructive pneumonitis; cancer in situ of left upper lobe bronchus at its division into apical posterior and anterior divisions	Died 3½ yr.*
3	M 62	"Virus pneumonia" followed by cough and intermittent hemoptysis	1 yr.	negative	Roughened mucosa right upper lobe bronchus; biopsy positive	Sputum positive for cancer cells; bronchial secretions: positive	Pneumonectomy, right lung (lung normal to palpation)	Extensive squamous cell carcinoma in situ over 3 cm. of right main and upper lobe bronchi	Died 1 mo. after operation†
4	M 67	No pulmonary symptoms; in situ S.C.E. of vocal cord treated 8½ yr. earlier; no residual	——	Pneumonitis, right upper lobe	Nodular mucosa right upper lobe bronchus; biopsy positive	Bronchial secretions: negative	Pneumonectomy, right lung	Carcinoma in situ, extensive involvement of right upper lobe bronchus and orifices of its 3 main subdivisions	Died 3½ yr. after operation; cause of death unknown
5	M 58	None referable to chest	——	Widening of mediastinum; possible pleural thickening on right	Blood noted coming from right upper lobe bronchus; no tumor seen; biopsy negative	Bronchial secretion from right upper lobe: positive for cancer cells	Pneumonectomy, right lung	Carcinoma in situ, with questionable infiltration of mucosa surrounding orifice of apical division right upper lobe bronchus	Alive and well 4 yr. after operation‡
6	M 52	Cold; chills followed by cough with some yellowish sputum	4 wk.	Exaggerated right hilar shadow with infiltration of adjacent right upper lobe	Mucosal abnormality, posterior lateral wall, right main bronchus; biopsy positive	Bronchial secretions: positive	Pneumonectomy, right lung	Carcinoma in situ, right main bronchus	Alive and well 8 yr. after operation

*Necropsy findings: subdiaphragmatic abscess; no evidence of carcinoma.

†Pulmonary embolism with infarction.

‡Carcinoma in situ of right bronchial stump developed 3 years after operation; x-ray treatment.

follows: group 1 — carcinoma in situ with no demonstrable infiltration or with minimal or equivocal evidence of infiltration (six cases), group 2 — carcinoma in situ with associated superficial infiltration extending maximally down to bronchial cartilages (five cases), and group 3 — carcinoma in situ with associated infiltration but not beyond the bronchial wall (four cases).

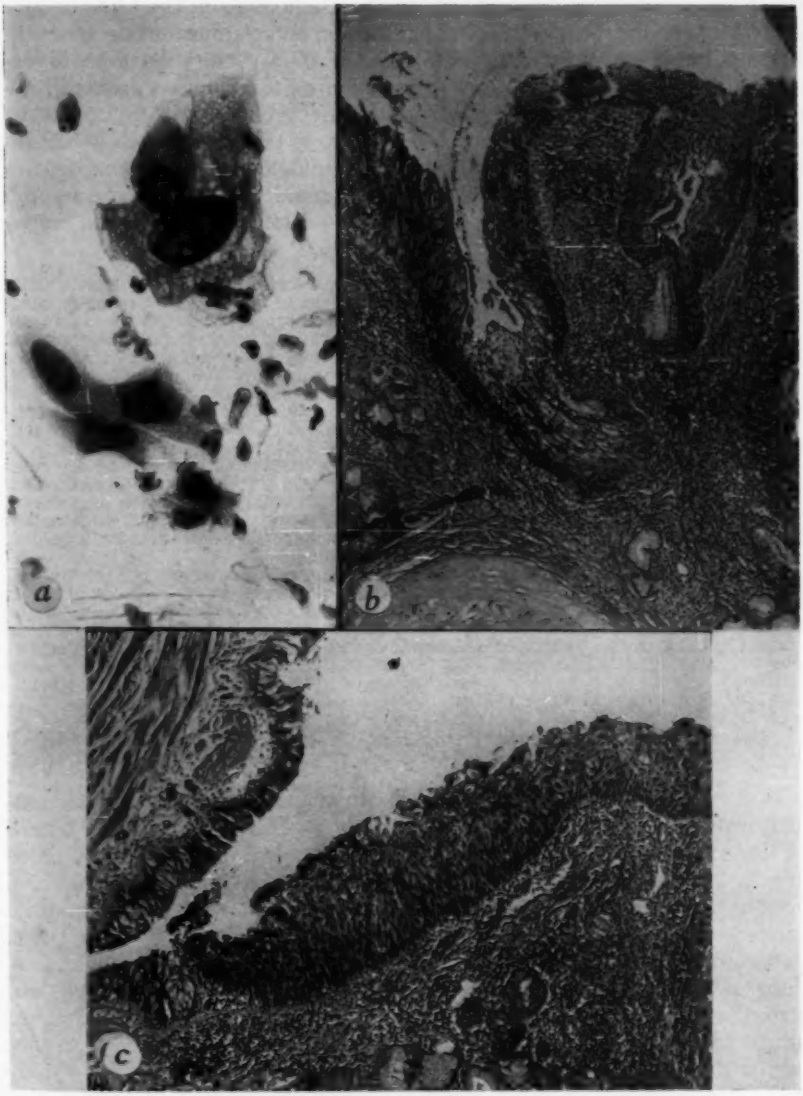

FIGURE 2 (case 1). *a*. Carcinoma cells (squamous type) in sputum (hematoxylin and eosin; x600). *b*. In situ squamous cell carcinoma of apical branch of left upper lobe bronchus. Ducts of mucous glands were involved but infiltration was equivocal (hematoxylin and eosin; x60). *c*. Higher magnification showing transition between normal and in situ carcinomatous surface epithelium (hematoxylin and eosin; x25).

Carcinoma In Situ, Group 1 (Six Cases)

In the six cases the resected carcinomas were considered to be entirely in situ or at most showing minimal or equivocal invasion (fig. 1*a* and *b*). A description of a typical case follows and the salient findings in all six cases are shown in table 1. In group 1 a diagnosis of bronchogenic cancer was based on finding carcinoma cells in the sputum followed by the demonstration of positive bronchial secretions from the affected lobe in two cases and on positive bronchial secretion alone in one case. In three other cases specimens obtained for biopsy from an area of abnormal mucosa seen on bronchoscopic examination showed positive findings. In these three cases, obstructive pneumonitis was found in the affected lobe in one case only. Of the three cases in which resection was carried out on the basis of positive cytologic findings with negative bronchoscopic examination, obstructive pneumonitis was present in only one case. In the other two cases the resected lobe was normal to palpation at the time of operation.

Case 1: A dry cough had developed in a 55-year-old white man 2 months prior to his arrival at the Mayo Clinic. A roentgenogram of the thorax had been interpreted as normal, but a specimen of sputum had been reported positive for carcinoma cells. Three bronchoscopic examinations had not disclosed a source of these abnormal cells. Bronchograms had been normal except for the lack of opaque medium in the bronchi of the left upper lobe. The thoracic roentgenogram made after the patient's arrival at the clinic revealed some evidence of emphysema of the apical segment of the left upper lobe but no mass could be detected in the left upper lobe. Otolaryngologic and bronchoscopic examinations gave normal results. The left upper lobe bronchus was carefully examined with the right-angled telescope at the time of bronchoscopy but no evidence of a lesion could be seen. The left upper lobe bronchus was irrigated with 10 cc. of normal saline solution and secretions were aspirated for cytologic study. The right side was also apparently normal to inspection and smears and secretions were removed for cytologic study. Results of cytologic examination for carcinoma cells included positive sputum (fig. 2*a*), positive washings from the left upper lobe and negative secretions from the right side.

Since cytologic and bronchographic evidence pointed to a carcinoma of the left upper lobe, surgical exploration was carried out. No tumor could be felt in the left upper lobe, but lobectomy was performed on the left upper lobe on the basis of the positive cytologic findings. Pathologic examination revealed a squamous carcinoma, grade 3 and 1.2 cm. in length, which surrounded the apical segment of the left upper lobe bronchus. The carcinoma was almost entirely in situ with involvement of ducts of mucous glands (fig. 2*b* and *c*). Serial block sectioning showed small areas of equivocal superficial infiltration. The hilar lymph nodes were not involved by tumor.

Bronchogenic Carcinoma In Situ With Superficial Infiltration, Group 2 (Five Cases)

In five cases the lesion, while largely in situ, was associated with definite mucosal infiltration which extended at most to the inner aspect of the bronchial cartilages. Clinical and pathologic data on these cases are shown in table 2 and one case (case 7) with evidence of an unusually prolonged in situ stage is reported briefly. A diagnosis of bronchogenic cancer was based on positive bronchoscopic specimens in two cases. In two cases the results of both cytologic and bronchoscopic examinations were negative and lobectomy was carried out for unexplained obstructive pneumonitis in a portion of the parenchyma of the involved lung. In one case positive sputum and bronchial secretions were obtained although the results of bronchoscopic examination were otherwise negative. In this case obstructive pneumonitis was present in the affected lobe. Pathologic examination revealed obstructive pneumonitis distal to the carcinoma in four cases while in the fifth case (case 7) no obstructive element was present.

Case 7: A 61-year-old man had had chronic asthmatic bronchitis of long duration associated with a small amount of mucoid sputum for many years. There had been no recent change in symptoms. A thoracic roentgenogram did not show evidence of any abnormality but cytologic examination of the sputum revealed carcinoma cells of squamous type (fig. 3*a*). The results of bronchoscopic examination and cytologic examination of bronchial secretions removed from each side of the bronchial tree were negative. A total of 13 specimens of sputum were examined during the ensuing 7 months and five gave positive results for carcinoma cells. Two additional bronchoscopic examinations as well as bilateral bronchograms failed to reveal any abnormality in the bronchial tree. Careful examination of the nasal passages including the nasopharynx, pharynx and larynx gave negative results and smears from these locations were normal cytologically.

By this time the patient began to doubt the validity of our studies, and he failed to return until 2 years and 9 months after the initial discovery of malignant cells in his sputum. In the interim mild asthmatic bronchitis continued unchanged. Roentgenograms of the thorax still did not show any abnormality (fig. 3*b*) but three specimens of sputum were positive for carcinoma cells. Bronchoscopic examination was advised but the patient deferred for 5 months. A mass was then seen in the left upper lobe bronchus and biopsy revealed a squamous cell carcinoma of grade 3.

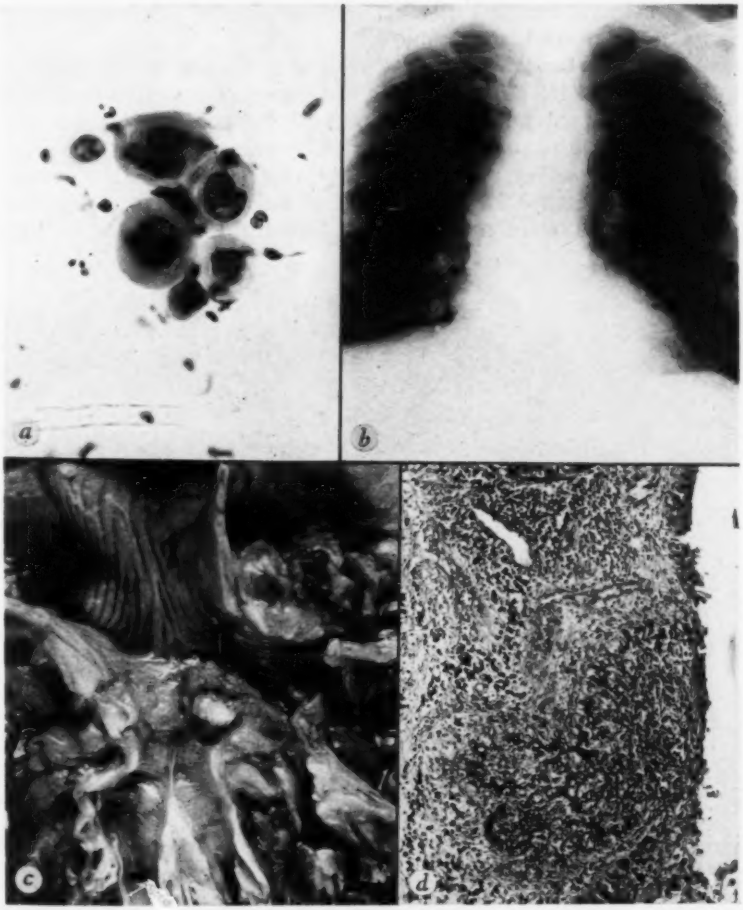

FIGURE 3 (case 7). *a*. Carcinoma cells (squamous type) in sputum (hematoxylin and eosin; reduced from x800). *b*. Roentgenogram of thorax considered negative 3 years after first positive sputum. *c*. Gross appearances of in situ and superficially infiltrative squamous carcinoma of right upper lobe bronchus. *d*. Histologic section through edge of lesion (hematoxylin and eosin; reduced from x120).

Bronchial secretions were positive for carcinoma cells. Thus, over a period of 3 years and 2 months, 20 sputum examinations were carried out, 10 of which gave positive results.

At the time of thoracotomy the surgeon was able to feel only a slight thickening in the region of the upper lobe bronchus. Left pneumonectomy was performed. Pathologic examination revealed a small squamous cell carcinoma of the left upper lobe bronchus which was in situ and infiltrative, extending to but not beyond the mucosal aspect of the bronchial cartilages (fig. 3*c* and *d*). No lymph nodes were involved and obstructive pneumonitis was not present. The patient has remained well up to the time of this report which is 2 years after pneumonectomy and 5 years after the initial positive findings in the sputum.

Carcinoma In Situ With Infiltration Limited to the Bronchial Wall, Group 3 (Four Cases)

Deeper infiltration of the lesion was found in this group but it did not extend into the surrounding pulmonary parenchyma. In most cases the infiltration was detected only on serial block sections, the bulk of the lesion being in situ or superficial (fig. 4*a* and *b*). Clinical and pathologic features are outlined in table 3.

Resection was based on positive results of biopsy in two cases, and in two cases positive secretions and associated obstructive pneumonitis were the significant preoperative findings. Pathologic examination revealed obstructive pneumonitis in all four cases. In case 12 the in situ change was extensive, involving the greater portion of the bronchial mucosa, while in case 11 the carcinoma was limited to a segment of the lingular division of the left upper lobe bronchus, 2 cm. in length.

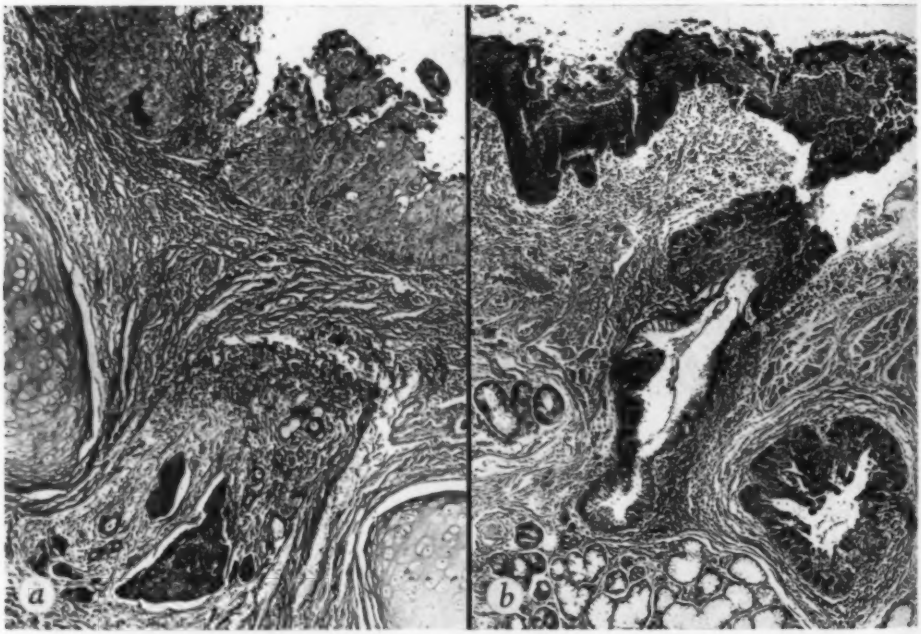

FIGURE 4. *a*. (case 13). Histologic section through lower lobe bronchus showing in situ carcinoma, also area of infiltration. The in situ change involved almost the entire bronchial tree with infiltration limited to the lower lobe bronchus (hematoxylin and eosin; x50). *b*. (case 15). In situ carcinoma involving surface epithelium and ducts of mucous glands. An area of infiltration extending almost through the bronchial wall was found on serial block section (hematoxylin and eosin; x60).

TABLE 2 — IN SITU AND SUPERFICIALLY INFILTRATIVE BRONCHOGENIC CARCINOMA

Case	Sex age (yr.)	Symptoms	Duration	X-ray of thorax	Result of bronchoscopic examination	Result of cytologic examination	Operation	Pathologic findings	Last report
7	M 61	"Chronic bronchitis"; no recent change in symptoms	Many years	Negative	Negative (3), positive (1)	Sputum, positive (3 yr.)	Pneumonectomy, left lung	In situ and superficially infiltrating squamous carcinoma, left upper lobe bronchus	Alive 5 yr.
8	M 73	Chronic cough; one episode of hemoptysis; pain right lower part of thorax	Many years; pain for 3 mo.	Poorly defined mass, superior segment of right lower lobe	Small tumor in superior segment of right lower lobe bronchus; biopsy positive	Bronchial secretions, positive	Lobectomy, right middle and lower lobes	In situ and superficially infiltrating squamous cell carcinoma, anterior orifice of superior division right lower lobe; obstructive pneumonitis	Alive 6½ yr.
9	M 63	Cough with sputum; episode of fever 1 month before examination	3 mo.	Lesion apical segment, right upper lobe	Right upper lobe retracted upward; purulent secretion; biopsy negative	Sputum and bronchial secretions, negative	Lobectomy, right upper lobe	In situs squamous cell carcinoma, 1.5 cm. in length, apical and posterior segments of right upper lobe bronchus; infiltration 1 mm. in depth	Alive 4 yr.
10	M 68	Pneumonic episode productive cough	1 mo.	Pneumonitis, left upper lobe	Negative	Sputum and bronchial secretions, positive	Pneumonectomy, left lung	Squamous carcinoma, 1 cm. in length at bifurcation of anterior and apical posterior divisions of left upper lobe bronchus; obstructive pneumonitis	Died in immediate postoperative period
11	M 49	No symptoms referable to thorax	——	Poorly defined mass, left upper lobe near hilus	No tumor seen; biopsy negative	Bronchial secretions negative	Lobectomy, left upper lobe	Squamous carcinoma, 1.5 cm. in length involving apical posterior branch of left upper lobe bronchus; obstructive pneumonitis	Alive 5 yr.

TABLE 3 — IN SITU AND INVASIVE BRONCHOGENIC CARCINOMA CONFINED TO BRONCHIAL WALL

Case	Sex age (yr.)	Symptoms	Duration	X-ray of thorax	Result of bronchoscopic examination	Result of cytologic examination	Operation	Pathologic findings	Last report
12	M 54	Episode of cold with pleuritic pain 6 wk. before examination; productive cough	6 wk.	Penumonitis, lingular portion of left upper lobe	Negative	Sputum and bronchial secretions in left upper lobe bronchus, positive	Pneumonectomy, left lung	Squamous carcinoma involving proximal 1.2 cm. of lingular division, left upper lobe	Died 3 yr.*
13	M 50	Symptoms of pneumonitis, fever, productive cough	3 wk.	Diffuse infiltration with linear fibrosis, base of right lung	Roughened mucosa, right bronchus intermedius; biopsy positive	Sputum and bronchial secretions, positive	Pneumonectomy, right lung	Extensive carcinoma in situ, right bronchial tree; infiltration in right lower lobe only	Alive and well 8 yr.
14	M 63	Episode chest cold; fever; slight pleurisy	3 mo.	Segmental pneumonitis, posterior division, right upper lobe	Negative, slight deformity, right upper lobe bronchus	Sputum and bronchial washings, negative	Lobectomy, right upper lobe	Squamous cell carcinoma partially in situ, partially invasive in right upper lobe bronchus	Alive 5 yr.
15	M 64	Nonproductive cough; one episode of hemoptysis	6 mo.	Pathologic process left lung extending out from hilus	Lesion with purulent secretion left upper lobe bronchus; biopsy positive	Bronchial secretions, positive	Pneumonectomy, left lung	Bronchial carcinoma in situ and infiltrative in left main bronchus	Alive 4½ yr.

*Coronary artery disease; no evidence of carcinoma.

Comment

Although few in number, these 15 cases represent the discovery and definitive treatment of bronchogenic carcinoma at an early and presumably curable stage of the disease. Symptoms relating to the thorax were entirely or virtually absent in four cases, while in the remainder cough, slight hemoptysis or more frequently an episode of pneumonitis was responsible for further investigation of the bronchial tree. The duration of symptoms, when present, ranged from 3 weeks to 7 months but in one case a pneumonic episode had occurred 1 year prior to the patient's admission to the clinic and in a second case the patient had noted hemoptysis 2 years prior to coming to the clinic.

Roentgenologic examination of the thorax gave normal results in two cases and in a third a widening of the mediastinum proved to be due to a tortuous aorta. In a fourth case, localized emphysema was the only abnormality noted. In the remaining 11 cases evidence of pneumonitis was substantiated by pathologic examination of the resected specimen. In all cases the shadow observed on the roentgenogram was apparently the result of varying degrees of associated peripheral pneumonitis rather than a tumor in the lung.

Cytologic examination of either sputum or bronchial secretions gave positive results in 11 of 15 cases (73 per cent). In case 7 positive cytologic findings had been noted for more than 3 years in spite of negative findings on repeated x-ray and bronchoscopic examinations. In two of four cases in which results of cytologic examination were negative, the results of bronchoscopic biopsy were positive; the results of bronchoscopic biopsy remained indetermined preoperatively in the other two cases and lobectomy was carried out because of unexplained obstructive pneumonitis.

Bronchoscopic examination gave a surprising number of positive results in spite of the absence of a visible tumor in the bronchial tree. Results of biopsy were positive in seven of 15 cases (47 per cent). In some cases no abnormality was seen but a random biopsy taken by the bronchoscopist proved to be positive while in others some roughening of mucosa or tendency toward excessive bleeding directed the bronchoscopist to the area of involvement.

Follow-up data would indicate that the lesion is curable at this stage of evolution, but the dangers of recurrence of carcinoma in situ in the stump are emphasized in case 5; in this case a superficial lesion or carcinoma in situ recurred in the stump 3 years after the patient's operation. Roentgen therapy was used and the patient had no evidence of residual tumor in the stump 1 year later. Two patients died in the immediate postoperative period. One patient died 3½ years after operation and necropsy showed the presence of subdiaphragmatic abscess. One patient died of coronary artery disease 3 years subsequent to operation and another patient died 3½ years after operation at the age of 72 years. In the latter case the cause of death was unknown but there was no known evidence of recurrence. The remaining nine patients are alive at the time of this writing from 4 to 8 years after operation without any known evidence of carcinoma.

SUMMARY

A small group of cases of bronchogenic carcinoma in situ or with associated early invasion have been reviewed. The results of cytologic examination were positive in approximately 73 per cent of cases and bronchoscopic biopsy was positive in 46 per cent. Although the condition of the patients has not been followed sufficiently long for thorough evaluation, highly favorable results of treatment in these early lesions are indicated.

RESUMEN

Un grupo pequeño de carcinoma broncogénico in situ o asociados a invasión temprana han sido objeto de revisión.

Los resultados del examen citológico fueron positivos en 73 por ciento aproximadamente de los casos y la biopsia a través del broncoscopio fué positiva en 46 por ciento.

Aunque la condición del enfermo no fué observada por tiempo suficientemente largo para una valoración completa indica que el tratamiento temprano de estas lesiones es altamente favorable.

RESUMÉ

Les auteurs ont étudié un petit groupe de cas de cancer bronchique in situ dont l'extension était très récente. Les résultats de l'examen cytologique furent positifs dans environ 73% des cas, et la biopsie par bronchoscopie dans 46%.

Bien que les malades n'aient pas été suivis pendant un temps suffisamment long pour une estimation complète, les auteurs ont état des résultats extrèmement favorables du traitement dans ces lésions précoces.

ZUSAMMENFASSUNG

Mitteilung einer kleinen Zahl von Fällen mit Bronchoscarzinom in situ oder mit von ihnen ausgehender frühzeitiger Metastasierung. Die Resultate der cytologischen

Untersuchung waren positiv in etwa 73% der Fälle und die bronchoskopische Biopsie war positiv in 46%.

Obgleich der Zustand der Patienten für eine grünliche Auswertung nicht genügend lange beobachtet werden konnte, werden besonders günstige Behandlungsergebnisse bei diesen Frühformen angegeben.

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Cavitary Carcinoma of the Lung: Roentgenologic Features in 19 Cases*

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The roentgenologic appearance of carcinoma of the lung may vary considerably from case to case. The tumor may obstruct a bronchus and cause atelectasis of a portion of a lung, it may grow as a mass in the hilus or in the periphery of the lung, or a mass may excavate and appear as a cavitary lesion. In this last form, carcinoma may simulate lung abscess and cyst. It is this cavitary form which we should like to emphasize because of the fact that it is probably more common than generally thought and because it is frequently confused with benign lesions and treated conservatively.

Liebow[1] wrote that "necrosis is common in bulky tumors. The liquefaction of necrotic tissue forms cavities in from 10 to 30 per cent of carcinomas." On the other hand, Strang and Simpson[2] found that only 3.6 per cent of 1930 carcinomas of the lung that they reviewed showed roentgenographic evidence of cavitation. The difference between these two figures is, of course, due to the fact that although the center of a tumor may be necrotic, this degenerated material may remain in place and not be discharged through a bronchus. Under such circumstances, although truly cavitary in nature from the standpoint of the pathologist, the roentgenologic appearance is not one of cavitation.

Liebow[1] also stated, "The cavity is almost always completely surrounded by tumor, and it is relatively rare to find an actual abscess cavity in the pneumonic tissue beyond the tumor." Openshaw[3] discussed two forms of cavity, namely the primary, in which the cavity is formed because of loss of tumor substance, and the secondary, in which the cavity is formed because of loss of nonmalignant pulmonary tissue. The secondary type is actually a suppurative abscess of the lung in an area of lung peripheral to a bronchus obstructed by the carcinoma. This latter form is undoubtedly quite rare and will not be considered further in this discussion.

In addition to the primary and secondary forms of cavitary carcinoma of the lung discussed by Openshaw, a third variety should also be mentioned. Rarely, a carcinoma may develop in the wall of a pre-existing benign bronchogenic cyst. We have observed one such case, and others have been reported in the literature.[4,5]

Material

A brief and incomplete review of the files of the Mayo Clinic disclosed 19 cases of cavitary carcinoma of the lung which were observed in the 5-year period September 15, 1953, to September 15, 1958. Material for microscopic examination had been obtained in all 19 cases and the pathologic type of tumor had been classified as follows: squamous cell

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epithelioma, 12 cases; large cell carcinoma, four cases; and adenocarcinoma, three cases (one of these was probably bronchiolar in origin) (fig. 1).

There were 17 males and two females. They ranged in age from 44 to 76 years. One individual was less than 50 years of age, five were in the sixth decade of life, seven in the seventh, and six in the eighth.

In all 19 cases, posteroanterior roentgenographic views of the thorax were available for review. Lateral views were available in 14 cases, tomograms in two cases, and roentgenograms made in the lateral decubitus position in four case

Roentgenologic Appearance

For the most part, the tumors were situated in the peripheral portions of the lungs away from the root of the lungs. All lobes were involved about equally except for the right middle lobe (RUL four cases, RML one case, RLL four cases, LUL four cases, and LLL six cases).

The tumors varied in size from one with a maximal diameter of 2 cm. to one with a greatest diameter of 12 cm. Thirteen of the masses were more than 5 cm. in diameter.

The cavities within the tumors also varied in size, as did the thickness of their walls. In a few instances, the wall was 1 mm. thick or less (fig. 1), while in several others the wall was thicker than 10 mm. In 11 of the 19 cases a fluid level was demonstrable roentgenologically, and in one instance two levels could be seen.

As has been said, the majority of the tumors were situated peripherally within the parenchyma of the lung. However, in four cases a bronchus of sufficient size was obstructed by the mass so that partial atelectasis of that segment of the lung resulted. In four instances the pleura was involved, as indicated by pleural thickening or the presence of pleural fluid. There was enlargement of the hilus of the affected lung in six of the 19 cases.

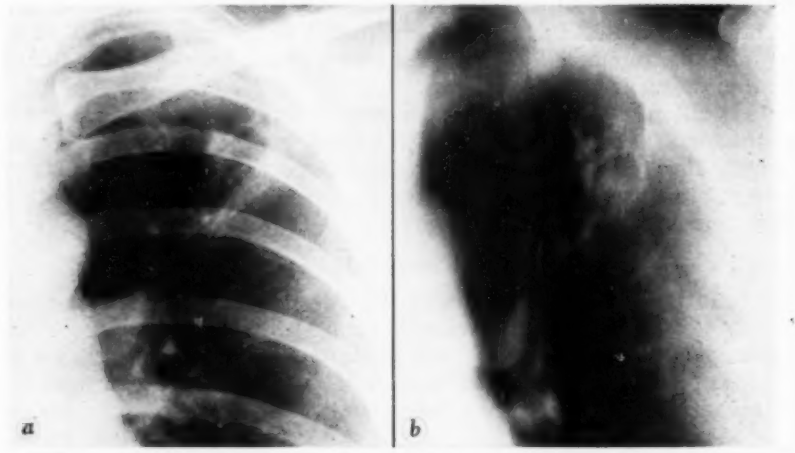

FIGURE 1. Cavitary adenocarcinoma, bronchiolar type, measuring about 2 cm. in its greatest diameter. *a*. Frontal projection. *b*. Tomogram. Note the thin wall and lack of fluid level.

One feature, described by others and observed in five of our 19 cases, was the existence of a solid mass attached to the wall of the cavitary lesion and situated within the cavity. This is illustrated in figure 2 and has been called the "mural nodule." This finding is highly suggestive of malignant noplasm and should serve to distinguish the lesion from the ordinary form of suppurative abscess of the lung or bronchogenic cyst.

From the standpoint of roentgenologic appearance, our cases fell into two broad groups: those simulating suppurative abscess of the lung and those simulating bronchogenic cyst. There were three cases in the

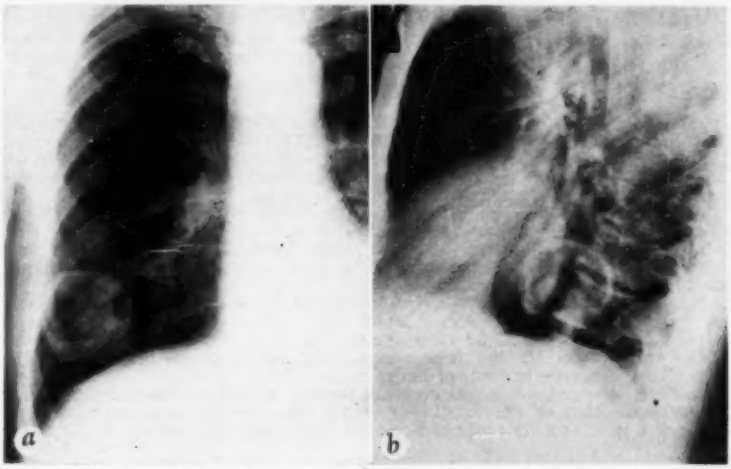

FIGURE 2. Cavitary squamous cell epithelioma simulating lung cyst. *a*. Frontal projection. *b*. Lateral view. Note the spherical shape, sharp borders, thin wall, fluid level and large mural nodule.

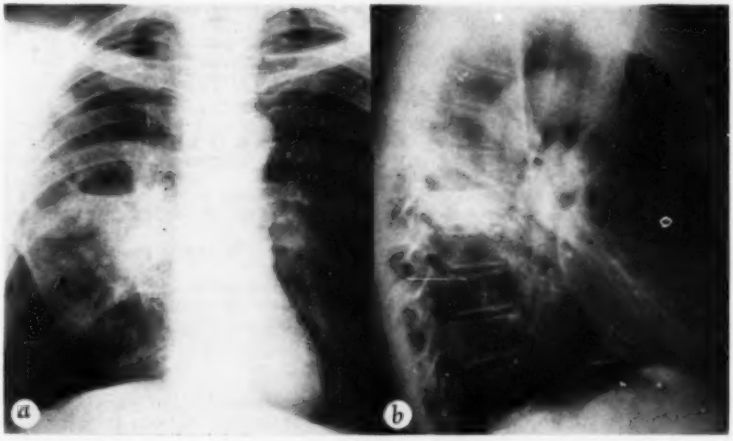

FIGURE 3. Cavitary squamous cell epithelioma simulating suppurative abscess of the lung. *a*. Frontal projection. *b*. Lateral view. Note location in superior segment of right lower lobe, fluid level, poor definition of borders, evidence of inflammation in neighboring lung and hilar enlargement.

latter group, and in each instance the lesion exhibited a sharp outline, was relatively spherical in shape, and had a thin wall (fig. 2). In all three cases, a mural nodule could be observed. A fluid level was present in two, but not in the third.

In the other 16 cases, the roentgenologic appearance was more suggestive of lung abscess (fig. 3). Generally, the borders were less sharp, the walls surrounding the cavity were thicker and less regular, and in 10 of the 16 instances a zone of inflammation was present in the adjacent lung. In only two instances were definite mural nodules demonstrated, although in several cases the interior surface of the wall of the cavity was irregular. One or more fluid levels could be demonstrated in 10 of these 16 cases.

Comment

In general, it can be said that carcinoma should always be considered seriously in the diagnosis of any cavitary lesion of the lung. This is especially true if the patient is in the "cancer age," that is, more than 40 years old. It is also especially true if the lesion is large and if there is no calcification roentgenologically demonstrable in the lesion or in the neighboring parenchyma of the lung.

Certain clinical symptoms and signs and the results of certain laboratory tests are valuable in making the proper diagnosis, but it is not the purpose of this paper to enter into a discussion of these. Mention should be made, however, of the value of cytologic examination of the sputum and bronchoscopic biopsy, both of which may provide a definite diagnosis of carcinoma.

It is well for physicians to be aware that a cavitary carcinoma does not always have a thick wall, as is sometimes taught. In three of our cases the wall was 1 mm. thick or less, yet pathologic examination disclosed that this very thin wall was made up entirely of tumor cells. It should be remembered, too, that the presence of a mural nodule is strong evidence in favor of malignancy.

The roentgenologic examination does not provide a certain diagnosis of carcinoma, but proper evaluation of the existing evidence may prevent prolonged conservative treatment of a neoplasm that is better treated by surgical removal.

SUMMARY

Carcinoma should always be considered seriously in the diagnosis of any cavitary lesion of the lung, especially if the patient is more than 40 years old and if the lesion is large and if there is no calcification roentgenologically demonstrable in the lesion or in the neighboring parenchyma of the lung. Cytologic examination of the sputum and bronchoscopic biopsy may provide a definite diagnosis of carcinoma. A cavitary carcinoma does not always have a thick wall. The presence of a mural nodule is strong evidence in favor of malignancy. Roentgenologic examination does not provide a certain diagnosis of carcinoma, but proper evaluation of the existing treatment of a neoplasm that is better treated by surgical removal.

RESUMEN

El carcinoma debe siempre tomarse en consideración para el diagnóstico de cualquiera lesión cavitaria en el pulmón, particularmente si el enfermo as mayor de 40 años, si la lesión es grande y si no hay calcificaciones demostrables a los rayos X en la propia lesión o en el parenquima cercano.

El examen citológico del esputo y la biopsia a través del broncoscopio, pueden proporcionar la confirmación del diagnóstico de carcinoma. Un carcinoma cavitario no siempre tiene pared gruesa.

La presencia de un nódulo en la pared cavitaria, es una fuerte presunción en favor de la enfermedad maligna.

El examen roentgenológico no proporciona un diagnóstico seguro del carcinoma, pere la estimación bien hecha de la evidencia existente puede evitar que s haga un tratamiento conservador prolongado en el caso de una neoplasia que es mejor tratada por la escisión quirúrgica.

RESUMÉ

Le cancer devrait toujours être pris en sérieuse considération dans le diagnostic de toute lésion cavitaire du poumon. Cetté proposition est surtout valable quand le malade est âgé de plus de 40 ans et la lésion volumineuse, et quand il n'y y pas de calcification radiologiquement mise en évidence dans la lésion ou dans le parenchyme pulmonaire voisin. L'examen cytologique de l'expectoration et la biopsie bronchoscopique peut apporter un diagnostic précis de carcinome. Un cancer cavitaire n'a pas toujours une épaisse paroi. La présence d'un nodule intramural est un argument

solide en faveur de la malignité. L'examen radiologique ne permet pas un diagnostic certain de carcinome, mais une juste estimation des arguments offerts par l'examen peut empêcher la prolongation d'un traitement conservateur d'une néoplasie qui devrait bénéficier d'une exérèse chirurgicale.

ZUSAMMENFASSUNG

Ein Carzinom muss man immer ernsthaft in Erwägung ziehen bei der Diagnose jedweder cavitären Veränderung der Lunge, besonders dann, wenn der Kranke mehr als 40 Jahre alt und wenn die Läsion umfangreich ist und sich eine Verkalkung röntgenologisch nicht nachweisen lässt im Bereich des Befundes oder im benachbarten Lungengewebe. Cytologische Untersuchung des Sputums und eine bronchoskopische Biopsie können zu einer definitiven Diagnose des Carzinoms führen. Ein Carzinom mit Cavernenbildung verfügt nicht immer über eine dicke Wand. Das Vorliegen eines wandständigen Knötchens spricht in hohem Masse zu Gunsten einer Bösartigkeit. Da röntgenologische Untersuchungen nicht immer zu einer sicheren Carzinom-Diagnose führen, kan eine sorgfältige Auswertung der vorliegenden Befunde die überlange konservative Behandlung eines Neoplasmas verhindern, das besser dadurch behandelt wird, dass es der Chirurg entfernt.

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The Prognosis in Idiopathic Diaphragmatic Paralysis*

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In the practice of thoracology the physician occasionally encounters a patient having complete paralysis of one of the hemidiaphragms. In some of these cases a detailed history and careful examination of the neck, thorax, and abdomen fail to disclose the cause of the disorder; such cases may be classified conveniently as "idiopathic."

A number of possible etiologic factors have been advanced in efforts to explain the cause of idiopathic unilateral diaphragmatic paralysis. Bingham[1] expressed the view that birth injury to the phrenic nerve is possible even without demonstrable injury to the brachial plexus. Couch[2] reported five cases in which he believed the paralysis had resulted from antecedent pneumonia. Lieberman[3] suggested a selective neuritis as the cause in some cases. Joannides[4] described a primary inflammation of the diaphragm. Kahn[5] cited the possibility of damage to central nuclei and to the paralyzing potentiality of neurotoxic infections or poisons.

Material and Methods

A survey of Mayo Clinic records of patients examined since 1935 yielded hundreds of instances of elevated hemidiaphragm not attributable to phrenic operations, but for the purpose of this study selection was limited to cases in which total paralysis had been demonstrated fluoroscopically. Fifty-nine cases satisfied these requirements; of these, 19 were set aside because of the existence of circumstances that reasonably could have been held responsible for the physiologic or anatomic disruption of one of the phrenic nerves. Such exclusions, with their numerical frequencies, are shown in the table. This group having been eliminated, our study was concerned with the remaining 40 cases, which could be considered examples of "pure" idiopathic diaphragmatic paralysis. Thirty-one of the patients were males, and 9 females. Their ages ranged from 11 months to 64 years, averaging 49 years. The paralysis was on the left side in 21 and on the right in 19.

Some kind of follow-up information was available from 35 (87 per cent) of the 40 patients. The intervals between the diagnosis and the latest observation ranged from 4 months to 19 years. These intervals exceeded 15 years in one instance (2.5 per cent), 10 years in 6 (15 per cent), 5 years in 16 (40 per cent), 2 years in 28 (70 per cent), and 1 year in 32 (80 per cent). Information as to the general state of health was available in 34 instances.

Opportunity to inspect a new roentgenogram of the chest and to compare it with older films was available in 27 instances, and in seven of the cases it was possible to re-examine the chest fluoroscopically. For purposes of analysis it was assumed that an unchanged roentgenographic appearance indicated no significant recovery of diaphragmatic function, and that a normal roentgenographic appearance indicated recovery of

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TABLE—REASONS FOR EXCLUSION

Reasons	Cases
Primary bronchopulmonary malignant lesion	6
Metastatic cervical or thoracic malignant lesion	3
Malignant tumor elsewhere in body	1
Significant pulmonary tuberculosis, active or inactive	2
History of any significant homolateral cervical or thoracic lesion, injury, or operation	7
Total	19

at least some degree of function on the affected side. It is possible that some of the patients whose films showed no change regained a degree of diaphragmatic function undetectable in so incomplete an examination as evaluation by roentgenographic means alone.

None of the traced patients died during the period covered by the study, though there were two deaths after the last observation, one allegedly due to a heart attack and the other of unknown cause.

Findings

Associated Symptoms and Conditions. — As it has been known[6] that unilateral diaphragmatic paralysis may exist without significant impairment of respiratory function, it may not be surprising that among the 40 patients only four complained of exertional dyspnea at the time of the examination in which the paralysis was discovered. Other associated thoracic conditions were recurrent hiccough in one patient, allergic bronchial disease in two, auricular fibrillation in one, and paroxysmal tachycardia in one.[1] One patient had idiopathic paralysis of the ipsilateral vocal cord and another had paralysis of the facial nerve on the same side and of the vocal cord on the opposite side. The other 29 patients had no symptoms and no associated findings of significance.

Health and Symptoms at Follow-up. — Among the 35 patients from whom information as to the state of health was available, 22 had no thoracic symptoms. Eleven reported significant exertional dyspnea, two reported recurrent thoracic pain, and one reported a sensation of pressure in the region of the affected hemidiaphragm. With the incomplete information available, it was not possible to determine whether any or all of these symptoms were results of the disorder of the diaphragm; but of the patients whose diaphragmatic function returned, only one complained of dyspnea.

New and Recent Roentgenologic Studies. — Among the 27 cases in which follow-up thoracic roentgenograms and sometimes fluoroscopic examination were available, no change in the height or function of the affected hemidiaphragm was discoverable in 18. The interval between diagnosis and last observation in this group ranged from 4 months to 14.7 years. In seven cases, with follow-up intervals ranging from 2 to 19 years, return of the diaphragm to normal position or function was evidenced by roentgenogram in four and by fluoroscopic appearances in two others. The seventh patient, last observed 4½ years after diagnosis, showed return of the affected hemidiaphragm to normal but marked elevation of the opposite hemidiaphragm, suggesting that he had re-

covered from his affliction only to have the same trouble develop later on the opposite side.

Beyond these 25 who clearly recovered or clearly did not, one patient, last observed at 2¼ years, exhibited the same elevation of the hemidiaphragm but with apparently normal respiratory excursion. One patient, last observed at 1½ years, exhibited the same degree of elevation as before but with the diaphragmatic mobility estimated at 50% of normal. These last two cases of the 27 suggest that significant return of function is possible without return of the hemidiaphragm to its normal position, and they tend to invalidate the thoracic roentgenogram alone as a sufficient basis of follow-up study in cases of diaphragmatic paralysis.

Regarding the date and speed of onset of idiopathic phrenic paralysis the study yielded only meager information, though enough to indicate that at least some of the cases were acquired and not congenital. In one patient fluoroscopic examination 2 years before the date of diagnosis had showed partial paralysis of the diaphragm; in another, a thoracic roentgenogram made 1 year before the date of diagnosis had not demonstrated abnormality. These two cases, added to the seven that exhibited return of phrenic function, give a total of nine affording definite evidence that the paralysis was acquired.

In only 1 case did late examination reveal a thoracic disorder which had not been present at the time of diagnosis and which conceivably might have been related to the paralysis: a roentgenogram made 5 years after the diagnosis showed calcified paratracheal nodes on the same side as the paralysis in a male patient 44 years old.

Treatment

Since hemidiaphragmatic paralysis of undetermined origin usually is asymptomatic, efforts at treatment seem unnecessary. In one case of this series, regarded as idiopathic until explored, an operation was performed on a man of 50 to establish the cause of the paralysis and correct it if possible. Exploration of the phrenic nerve showed it to traverse a dense fibrotic mass. From this it was freed by dissection. Partial return of diaphragmatic function was noted during his convalescence, and the same incomplete but improved mobility was noted in a re-examination 2½ years later. (This case is not included in the follow-up records).

Comment

Unexplained interruptions of nerve function — apparently similar to that assumed in idiopathic diaphragmatic paralysis — are noted also in cases of Bell's palsy and those of idiopathic paralysis of one of the vocal cords. Pickerill and Pickerill[7] have written that spontaneous recovery occurs in 75 to 90 per cent of cases of Bell's palsy, but Huppler and associates[8] found that the chance of spontaneous recovery of the voice after idiopathic paralysis of one of the recurrent laryngeal nerves is one in three. As mentioned, some degree of recovery eventuated spontaneously in nine of 27 traced cases of our series. The natural history of the three conditions seems sufficiently similar to suggest that their originating causes may be related.

SUMMARY

Forty cases of idiopathic diaphragmatic paralysis were studied in an effort to learn something of the permanence of the condition. Follow-up information was available in 87 per cent, including roentgenologic evidence in 68 per cent. None of the patients died or had serious illness during the period of observation, which ranged from 4 months to 19 years. Twenty-six per cent of the traced patients exhibited spontaneous return of the diaphragm to apparently normal function, as evidenced by re-examination after intervals ranging from 2 to 19 years. The findings indicate that idiopathic

diaphragmatic paralysis is a benign condition, and that without untoward associated findings unilateral idiopathic phrenic paralysis is seldom, if ever, a harbinger of serious disease. Further, the study suggests that in phrenic paralysis there is a likelihood of at least 25 per cent that complete or partial recovery of normal diaphragmatic function will occur spontaneously.

RESUMEN

Se estudiaron cuarenta casos de parálisis diafragmática idiopática tratando de averiguar algo sobre la permancia de esa parálisis. Se pudieron seguir en el 87 por ciento con evidencia roentgenológica en 68 por ciento.

Ninguno de los enfermos falleció o tuvo enfermedad grave durante el período de observación que fué de 4 meses a 19 años. Veintiseis por ciento de los enfermos seguidos mostraron regresión espontánea de la función diafragmática aparentemente a lo normal, según se demostroó al volverlos a examinar después de 2 a 19 años.

Estos hallazgos indican que la parálisis diafragmática idiopática constituye una afección benigna y que, no habiendo otros hallzgos desfavorables asociados, la parálisis frénica rara vez si acaso es precursora de una enfermedad grave. Más aún, el estudio sugiere que en la parálisis frénica hay una posibilidad por lo menos de 25 por ciento de que se logra la recuperación completa o parcial de la función diafragmática, de manera espontánea.

RESUMÉ

40 cas de paralysie diaphragmatique idiopathique furent étudiés dans le but de tirer quelque enseignement de la longue surveillance de cet état. Des indications provenant de contrôles réguliers purent être utilisées dans 87% des cas, dont 68% contrôles radiologiquement. Aucun des malades ne mourut ou n'eut de maladie grave pendant la période d'observation qui s'étendit de 4 mois à 19 ans. Chez 26% des malades suivis on assista à un retour spontané de la fonction apparemment normale du diaphragme. Ceci fut mis en évidence par de nouveaux examens à des intervalles qui s'étageaient de 2 à 19 ans. Ces constatations font la preuve que la paralysie diaphragmatique idiopathique est un état bénin et que sans autres éléments associés, elle est rarement, et même pour ainsi dire jamais, le signe précurseur d'une affection grave. D'ailleurs, cette étude permet de penser qu'il est vraisemblable qu'au mois 25% des paralysies phréniques retrouveront spontanément de façon complète ou partielle une fonction diaphragmatiique normale.

ZUSAMMENFASSUNG

40 Fälle idiopathischer Zwerchfellähmung wurden untersucht im Hinblick darauf, etwas in Erfahrung zu bringen über die Dauer dieser Affektion. Angaben über Nachbeobachtungen standen in 87% zur Verfügung mit röntgenologischen Befunden bei 68%. Keiner der Kranken verstarb oder erlitt eine enrsthafte Erkrankung während der von 4 Monaten bis zu 19 Jahren betragenden Beobachtungszeit. 26% der weiter verfolgten Kranken zeigte eine spontane Rückkehr des Zwerchfells zu augenscheinlich normaler Funktion, wie sich durch Nachuntersuchungen in Intervallen zwischen 2 und 19 Jahren ergab. Die Befunde weisen darauf hin, dass die idiopathische Zwerchfellähmung eine harmlose Affektion ist und dass ohne ungünstige Nebenumstände die einseiting idiopathische Phrenikuslähmung selten, wenn überhaupt, ein Vorläufer einer schwereren Krankheit darstellt. Ferner legt das Untersuchungsergebnis die Vermutung nahe, dass bei der Phrenikuslähmung eine Wahrscheinlichkeit von wenigsten 25% defür vorhanden ist, das spontan eine komplette oder partielle Wiederherstellung der normalen Zwerchfellfunktion eintreten wird.

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Thoracic Surgery in the Aged*

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The increase in longevity of our population has introduced new problems in the fields of medicine and surgery. Many authors have already contributed to the literature on geriatric surgery.[1-6] Most of the reports have dealt with general surgery. Cole,[2] in an extensive review of this subject, found that in certain surgical procedures the mortality rate of patients older than 60 years was not significantly greater than that of younger patients, but that in such operations as colostomy, esophagectomy, radical oral and neck surgery, pneumonectomy, and radical excision of the rectum, the mortality rate was significantly higher in the aged. It is the consensus of the various authors that elderly patients tolerate limited surgical procedures rather well, but they do not tolerate extensive operations as well as younger patients. Similarly, it has been found that the mortality rate is significantly higher in the presence of any concurrent disease such as hypertension, cardiac disease, or evident generalized arteriosclerosis. The mortality rate is doubled or tripled when operations must be carried out as emergency procedures. Because of the importance of recognizing concomitant disease and attempting to lessen the significance of such disease by appropriate therapy before operation, the close co-operation between the surgeon and the medical specialist has been stressed.

While the problem of general surgery in the aged has received appropriate attention, less has been written concerning intrathoracic surgery in the same age group. Campbell and Langston[7] reported their experience with 31 patients older than 60 years who underwent intrathoracic surgical procedures. There were two deaths in this group (6.5 per cent). Their series included 23 patients with malignant disease and eight patients with benign disease. They did not encounter more than average postoperative morbidity. They tended to make their operations as conservative as permissible. Their conclusions were that the average elderly patient tolerates extensive intrathoracic operations rather well. They considered mental alertness and good exercise tolerance as favorable signs. In his series, Cole[2] reported on eight patients more than 60 years of age who underwent lobectomy with no deaths, 18 who underwent pneumonectomy with a mortality rate of 27.7 per cent and 29 who underwent merely thoracic exploration with a mortality rate of 6.8 per cent. The mortality rates for lobectomy and thoracic exploration compared favorably to rates in the younger age group, but in the pneumonectomy series, the mortality rate was slightly more than twice that in the patients less than 60 years of age.

The increasing frequency with which we are being called on to consider thoracic operations in older patients made it desirable for us to review our experience with this problem and to make an effort to gain

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some knowledge of factors which might help in making recommendations concerning surgical measures. It is evident that chronologic age is not the most accurate means of categorizing these patients, but it is the most practical. We have chosen to include patients who were 70 years of age and older.

On review of the records of the Mayo Clinic during the 10-year period, 1947 through 1956, we were able to find 61 patients who had undergone 62 thoracotomies with pulmonary resection. One patient had undergone two operations: right upper lobectomy for squamous cell carcinoma and, 1½ years later, removal of the remaining two lobes because of a recurrence in the bronchial stump. The average age of the patients was 71.3 years. The oldest patient was 79 years of age. He underwent right lower lobectomy for squamous cell carcinoma and is alive at the time of this writing three years later. Fifty-three patients were men and eight were women. The average period of hospitalization in 48 cases was 11.6 days.

By far the greatest number of operations was carried out for malignant disease of the lung (table 1). Primary cancer of the lung was present in 48 patients and metastatic cancer in three patients. In approximately half of the patients with primary cancer of the lung a diagnosis of malignant disease had been established prior to operation. Of interest are the facts that the incidence of squamous cell carcinoma in this series is almost twice that reported by Kirklin and associates[4] for all age groups and that no case of small cell carcinoma was encountered. The one patient who was found to have tuberculosis had undergone lobectomy for an indeterminate lesion in the right middle lobe. With antituberculosis chemotherapy this patient lived almost 6 years after operation; he underwent prostatic resection and nephro-ureterotomy elsewhere and ultimately died of an unrelated disorder.

The total mortality rate in this series included all deaths occurring within one month of the date of operation. Because a number of patients died shortly after dismissal from the hospital we felt it would not reflect the true status if only the deaths occurring during the period of hospitalization were considered. The total mortality group consisted of 11 patients (17.7 per cent) (table 2). Seven of the 11 patients died during

TABLE 1—LESIONS FOR WHICH PULMONARY RESECTION WAS CARRIED OUT

Lesion			Number of Cases
Primary cancer			48
Bronchogenic carcinoma		47	
Squamous cell	(65.9 per cent)		
Large cell	(23.4 per cent)		
Adenocarcinoma	(10.6 per cent)		
Alveolar cell		1	
Metastatic cancer			3
Abscess			3
Unresolved pneumonia			2
Granuloma			2
Mineral oil granuloma			1
Tuberculosis			1
Broncholithiasis			1

hospitalization. The mortality rate of the group that underwent pneumonectomy was 29.6 per cent (eight patients). The number who had right and left pneumonectomies was about equal. Eleven underwent operation in which two lobes were removed. One patient died, and the mortality rate for this group was 9.1 per cent. The mortality rate for the 24 patients undergoing lobectomy or segmental resection was 8.3 per cent (two deaths). Thus, in this small series the difference between the mortality rate for the group that had one lobe removed and the rate for the group that had two lobes removed was not significant.

An attempt was made to evaluate the factors which might have been involved in the causation of the seven hospital deaths. In two patients, death was due to widespread metastasis not recognized preoperatively. These two patients suffered postoperative hypotension which was unresponsive to therapy. Another patient died immediately after removal of one lung from obstruction of the remaining lung by secretions. Two patients were considered to have died as a result of cardiac disease and, in addition, one of these patients was considered to have respiratory insufficiency following pneumonectomy. One patient died suddenly in an otherwise normal postoperative course. Necropsy was not performed. Another patient had hemiplegia following surgical intervention and died 3 days later. The presence of metastasis to the brain had been considered in this patient prior to operation.

At this point in our study we attempted to evaluate the preoperative physical condition of these seven patients and to determine whether or not the fatal outcome could have been predicted. In five patients who died in the hospital after operation some abnormality which obviously was not due to the primary disease had been noted during the preoperative physical or laboratory examination. These abnormalities ranged from an abnormal electrocardiogram or obesity to the possible presence of cerebral metastasis. In four patients, the abnormality noted before operation could have been a clue to the ultimate cause of death. During the preoperative evaluation none of the abnormalities were considered to represent a significant problem. Of the four who died shortly after dismissal from the hospital one had experienced atrial fibrillation after operation, one had had sufficient difficulties with retained bronchial secretions to require tracheostomy, and another had respiratory insufficiency and cardiac failure at the time of dismissal. The fourth died of pulmonary embolism.

Postoperative complications developed in 30 patients (table 3). In two instances transurethral resection had to be carried out to relieve urinary retention. There was little difference in the incidence of pul-

TABLE 2—PULMONARY RESECTION IN 61 SEPTUAGENARIANS (62 OPERATIONS): MORTALITY RATE

Operation	Number of operations	Deaths			
		Hospital		Total*	
		Number	Per Cent	Number	Per Cent
Pneumonectomy	27	5	18.5	8	29.6
Bilobectomy	11	1	9.1	1	9.1
Lobectomy	24	1	4.2	2	8.3
Total	62	7	11.3	11	17.7

*Total mortality included all deaths within 1 month after operation.

monary complications after pneumonectomy and lobectomy although the over-all complications were somewhat more numerous in the pneumonectomy group. These complications are neither unusual nor excessive and could be those of a group of younger patients undergoing the same type of operation.

Follow-up information has been obtained on most of these patients within the past year (1957). For the other patients follow-up time was calculated from the time the patient was last heard from or seen. At the time of this writing one patient has survived 5 years and seven patients (17.0 per cent) have survived 3 years.

Of the 10 patients who underwent operation for a nonmalignant condition, seven lived on an average of 4.4 years after operation. The longest period a patient has lived postoperatively is 6 years, 7 months.

TABLE 3—POSTOPERATIVE COMPLICATIONS AMONG 54 PATIENTS WHO LEFT HOSPITAL

Complications		Number of patients
Retention of secretions		5
Tracheostomy	2	
Bronchoscopy	1	
Urinary retention		4
Atrial fibrillation		4
Difficulty in re-expanding lung		4
Cardiac failure		2
Mental confusion		2
Shock		2
Bronchopleural fistula, empyema		1
Oversedation		1
Melena		1
Gastric dilatation		1
Prolonged fever		1
Respiratory insufficiency		1
"Slow" recovery		1

Comment

It should be mentioned at the outset that the patients comprising this study represent a select group. Undoubtedly there have been other patients in this age group who were refused operation because their general medical condition was such that surgical procedures could not be considered.

The primary goal of this investigation is to determine how well elderly people tolerate pulmonary resection. Hence, our main interest lies in the mortality and morbidity statistics. The mortality rate of 17.7 per cent in our series is higher than that reported by Campbell and Langston.[7] However, the two studies are not entirely comparable, because Campbell and Langston included patients 60 years of age and older. Our mortality rate for pneumonectomy (29.6 per cent) was similar to that reported by Cole (27.7 per cent), whose series also included patients in the seventh decade of life.

These statistics must be compared to the mortality figures for the same type of operation in all age groups before conclusions can be drawn concerning the relative operative risk of this age group. Undoubtedly, the current mortality rates for thoracic operations are lower than the rates reported in the literature, but inasmuch as our series extends back several years it is proper to compare it to other series collected over the same period. The mortality rate for lobectomy seems to be rather consistently between 5 and 14 per cent, with most authors reporting around 8 per cent for carcinoma of the lung.[9-11] This rate is lower in operations for tuberculosis.[12] From these figures it can be seen that the removal of one or two lobes in our group of patients was attended by a mortality rate not beyond that expected in an average group of patients. However, the same does not appear to be true for pneumonectomy, in which the operative mortality rate in the treatment of cancer of the lung in all age groups ranges from 11 to 25.9 per cent.[9-13] It should be stated that the mortality rate of 25.9 per cent was calculated on all deaths in a 2-month period after operation

and that 15 per cent strikes a fairly good average. Kirklin and associates[9] reported a mortality rate of 13.6 per cent for curative pulmonary resection. This included all degrees of resection. Thus it is apparent that our mortality rate of 29.6 per cent for pneumonectomy in this age group is considerably higher than the rate in younger patients.

Sorensen and associate[10] have stated that the poor prognosis and high operative mortality in resectional pulmonary operation for carcinoma in patients 70 years of age and more have made them "less aggressive." The mortality rate for penumonectomy supports their position. We might ask ourselves, "Are we justified in recommending surgical procedures to a patient in his seventies if it is apparent that pneumonectomy may be required to remove the tumor?" Perhaps we should advise some form of nonsurgical palliative treatment and spare the patient the risk of operation. However, it is difficult to deny a patient the one opportunity for cure for the reason of age alone.

We believe that the mortality rate for pneumonectomy can be made more acceptable by more careful selection of patients and more careful preoperative and postoperative care. In general, this program of care must begin at the time of examination of the patient. Attention should be given to minor physical and laboratory abnormalities which might not cause great concern in a younger patient. Preoperative treatment, when indicated and when possible, should be rendered to make the patient's physical condition as nearly ideal as possible. For example, a period of abstinence from smoking before operation is most desirable in an effort to reduce bronchitis and bronchial secretions. Preoperative bronchodilator therapy, use of iodides, and antibiotic therapy in those instances in which infection is considered to play a role are of value before operation in patients having mild asthmatic bronchitis. Cerebral symptoms should be viewed with great suspicion as possible indications of metastasis.

Not infrequently these patients have been on a restricted diet for medical or other reasons, have been given digitalis and diuretics for dyspnea or edema of the ankles, or have been taking steroids for "arthritis." Such information must be sought by direct questioning. Many times the patient has forgotten about this medication or has considered it irrelevant. The serum proteins should be determined in those patients giving a history suggesting inadequate dietary intake. A commoner finding is an electrolyte disturbance resulting from salt restriction or diuretic therapy. It may be necessary to increase the oral intake of sodium chloride and potassium before operation. Before operation any digitalis therapy should be evaluated as to need, type and amounts because after operation, if digitalis is needed, the patient may not be able to furnish such data as accurately as preoperatively and determination of dosage becomes more difficult. Electrocardiographic evaluation is helpful. Steroid therapy prior to operation, to avoid adrenocortical insufficiency resulting from the stress of surgical procedures, may be indicated if the patient has received suppressive doses of steroids within the preceding 3 months. Careful observation for evidence of adrenocortical insufficiency is indicated in all patients who have received steroids within the preceding year.

After these data are obtained the internist and surgeon are in a position to decide as to whether or not the patient is a reasonable surgical risk. We cannot offer hard and fast rules which will enable the surgeon to make this selection with ease and confidence. Obviously, moderate or severe coronary insufficiency, congestive heart failure, significant pulmonary insufficiency resulting from diffuse pulmonary disease, and symptomatic cerebral atherosclerosis preclude surgical intervention. Also, the presence of other disease which is expected to shorten life expectancy significantly should influence one in giving advice concerning pulmonary resection. Much depends on clinical impression. It is a discouraging sign if the intangible factor of the desire to live is not present.

We concur with the opinions of Campbell and Langston[7] who advocated limiting the extent of resection as much as permissible. In view of the lack of agreement concerning the value of pneumonectomy as opposed to lobectomy in the surgical treatment of cancer of the lung,[14] we are not of the opinion that the increased risk attending pneumonectomy is justifiable if a lesser resection will suffice.

The postoperative care of patients whose reserves are limited also requires close supervision. Early evidence of retention of secretions should be detected and vigorous treatment rendered. Tracheal aspiration or bronchoscopy may suffice in a younger patient, but tracheostomy in the older patient permits an ideal route for evacuation of bronchial secretions as well as providing a most satisfactory stoma for assisting ventilation with a mechanical respirator if necessary. It is felt that tracheostomy should be done early to avoid the serious complications of bronchial obstruction and inadequate ventilation. The late use of tracheostomy becomes only a useless gesture. Sedatives and fluid therapy should be used with care. By constantly reminding ourselves that these patients have limited reserves and that we should tax these reserves as little as possible, we hope to be able to reduce the mortality rate in aged patients.

Conclusions

Patients 70 years of age and older tolerate limited pulmonary resection well but do not tolerate pneumonectomy well. Pulmonary resection in this age group should

be as limited as is possible. Careful selection of patients, careful preoperative preparation and close postoperative supervision are necessary in handling aged patients whose reserves are limited.

RESUMEN

Los enfermos de 70 o más años toleran bien la resección pulmonar limitada pero no toleran bien la neumonectomía. La resección pulmonar en esta edad debe ser tan limitada como sea posible. La selección cuidadosa de los enfermos, el cuidado preoperatorio minucioso y la vigilancia postoperatoria son necesarios para estos enfermos cuyas reservas son restringidas.

RESUMÉ

Les malades âgés de 70 ans ou davantage tolèrent bien une résection pulmonaire limitée, mais ne tolèrent pas bien une pneumonectomie. La résection pulmonaire chez les malades de cet âge devrait être aussi limitée que possible. Un choix judicieux des malades, une pré-paration préopératoire prudente et un contrôle post-opératoire précis sont nécessaires lorsqu'on prend en main des malades âgés, dont les réserves sont limitées.

ZUSAMMENFASSUNG

Kranke min einem Alter von 70 Jahren und mehr vertragen wohl Lungenresektionen in begrenztem Umfang gut, aber keine Pneumonektomien.

Die Lungenresektion in dieser Altersklasse muss so weit wie irgend möglich begrenzt werden. Sorgfältige Auslese der Kranken, sorgfältige Vorbereitung zur Operation und eine genaue postoperative Kontrolle sind erforderlich bei der Behandlung bejahrter Patienten, deren Reserven begrenzt sind.

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Adjustment of Stores of Carbon Dioxide During Voluntary Hyperventilation*, **, †

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Carbon dioxide is stored in the body in various forms, including carbonic acid, bicarbonate and carbamino compounds. The various stores of CO_2 can be considered to be in the lung, blood, soft tissues and bone. In an adult human, these stores are thought to be in the order of 120 liters of CO_2.[1] It is common knowledge that hyperventilation will reduce the level of CO_2 in the blood; however, only a small fraction of the total CO_2 of the body is in the blood. Questions arise, then, as to how much CO_2 can be eliminated by hyperventilation, from where does it come and in what manner does elimination proceed.

Several studies have been made of exchanges of CO_2 in animals and in man. In 1916, Liljestrand[2] found within the first hour of hyperventilation by men that 0.8 to 1.0 liter of stored CO_2 was eliminated for each 1 per cent decrease in alveolar concentration of CO_2. Brocklehurst and Henderson,[3] and Adolph and associates[4] subsequently derived widely varying values for the CO_2 capacity of the body. Several investigators have studied the CO_2 stores of animals.[1,5-9] From hyperventilation experiments on anesthetized dogs, Farhi and Rahn[1] found that alveolar CO_2 tension declined in an exponential manner and calculated that one half of the readily available stores of CO_2 was eliminated in 4 minutes.

The present study was undertaken to obtain additional information on the rate of elimination of CO_2 during hyperventilation in man, which might contribute to an eventual better understanding of clinical conditions such as CO_2 retention and narcosis.

Methods and Procedures

For analysis of the rate of elimination of CO_2, it was necessary that hyperventilation, once begun, be maintained at a constant rate. This could not be achieved with a cuirass respirator used on relaxed humans but was obtained in trained subjects as follows. Compressed air of known composition flowed at a constant rate into a spirometer balanced to prevent outflow except during inspiration (fig. 1). By observing the spirometer and maintaining it at a constant average volume, the subject could keep his respiratory minute volume equal to the constant rate of inflow of compressed air.

The subjects were three trained male physicians. After they sat at rest for 10 to 15 minutes, and in two experiments after an overnight fast, a small mask was applied and normal breathing was continued,

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with the flow of air adjusted to equal the spontaneous normal minute volume. Expired gases were directed through an infrared carbon dioxide analyzer* and an expiratory valve to a series of large-bore stopcocks that permitted collection of gas in any of five evacuated neoprene bags† (fig. 1). After 15 minutes, a forced maximal expiration was made following a 24-second period of breathholding at the end-normal inspiratory level. This permitted equilibration of CO_2 between alveolar gas and mixed venous blood and analysis of the CO_2 tension thereof. Natural breathing was then resumed for 10 to 15 minutes, and expired gases were collected for the last 5 minutes in the distal bag. At a predetermined signal, the flow of compressed air was suddenly increased and the subject breathed at a comfortable rate and depth such as to maintain the spirometer recording between two parallel lines previously drawn on the recording drum. The average minute volume for successive collection periods of 5 to 10 minutes was constant within about 1 per cent for intervals up to 64 minutes. While gases were being collected in one bag, the volume of contents of another was measured in a 120-liter spirometer, and samples were taken for analysis of oxygen and CO_2 by the Haldane apparatus. All expired gases were collected throughout the experiment over individual periods of 5 to 10 minutes. At the end of hyperventilation, breathholding and maximal exhalation were repeated as before, for estimating the mixed venous CO_2 tension. For two subjects, the difference between end-tidal and mixed venous tension esti-

*Liston Becker Model 16 (modified sampling cell), Beckman Instrument Company, Springdale, Connecticut.
†Darex balloons, Dewey and Almy Chemical Company, Cambridge, Massachusetts.

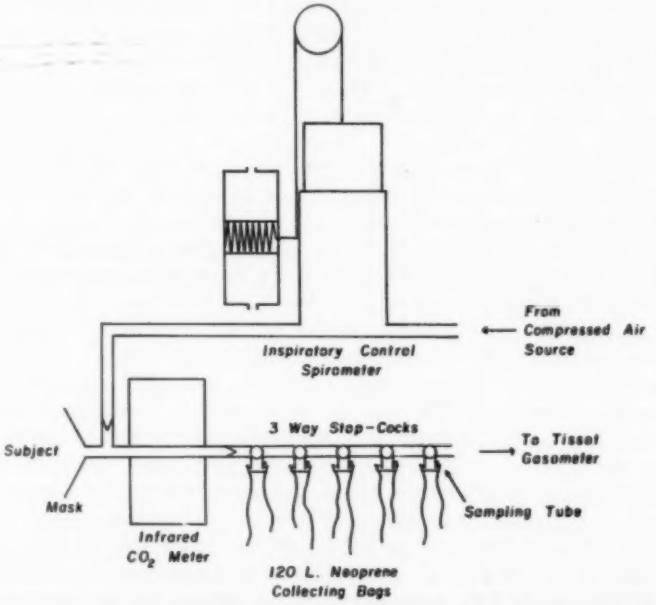

FIGURE 1: Diagram of apparatus for collecting expired gases during constant voluntary hyperventilation.

mated by breathholding agreed within 1 mm. of mercury with the difference as estimated by the more complex indirect procedure of DuBois and co-workers.[10]

During rest and hyperventilation, end-tidal, or alveolar, CO_2 tension was recorded continuously with the CO_2 meter and an Esterline Angus recorder (0.2-second response time). The meter was calibrated for each experiment with known gas mixtures and provided accuracy within 0.5 mm. of mercury. A volume of 430 ml. was required for complete flushing of the mask and meter. When this was added to the 320 ml. needed to purge the subject's dead space,[11] an expired volume of at least 750 ml. was considered necessary to provide samples in the meter equal in composition to end-tidal gas sampled at mouth level. Experimentally determined correction factorsw ere applied to the recorded CO_2 values for tidal volumes less than 750 ml., which occurred only in some control periods before hyperventilation.

From the volume and composition of expired gases, the exchange of oxygen and CO_2 was determined for each period. The total exchange equals the sum of the metabolic exchange and any change of bodily stores. The latter is negligible during the resting steady state preceding hyperventilation. The metabolic production of CO_2 during the later periods of hyperventilation, including that produced by the work of breathing, was defined as that quantity of CO_2 necessary to maintain the exchange ratio (R.Q.) of expired gas equal to that ratio observed prior to hyperventilation. Thus, the rate of oxygen uptake measured during hyperventilation could be multiplied by the initial exchange ratio to estimate the rate of metabolic production of CO_2 for the same period.[2,4,5,7] This was estimated differently for about the first 10 minutes of hyperventilation, because the rate of oxygen uptake increased immediately with the onset of hyperventilation but returned toward the resting value within 10 minutes. The initial increase of oxygen uptake was attributed chiefly to its accumulation by the bodily stores, and the return to near resting values was interpreted as the end of accumulation. During accumulation of oxygen stores, the metabolic uptake of oxygen was considered equal to the values obtained during the 5 to 10-minute period following the apparent end of accumulation. For studies in which hyperventilation was maintained for 10 minutes or less, the metabolic uptake of oxygen was considered equal to the resting value plus 2.6 ml. per liter per minute of excess ventilation.

The change of "whole body" stores of CO_2 was calculated for each period by subtracting the calculated metabolic production of CO_2 from the total quantity of CO_2 that was collected. For total periods of 20 and 60 minutes, this difference was divided into the changes of stores in the lungs, blood and tissues. The change of "lung stores" (strictly, of alveolar gas and not of pulmonary tissue) equaled the measured change of concentration of alveolar gas multiplied by the functional residual capacity, measured separately. The change of "blood stores" equaled the blood volume, assumed to be 80 ml. per kilogram of body weight, multiplied by the change in CO_2 content of blood corresponding to the observed change in CO_2 tension of mixed venous blood, obtained from a standard dissociation curve for oxygenated blood.[12] This procedure is

somewhat incorrect because the change of content of arterial blood probably exceeds that of venous blood, but the error is probably less than 10 per cent because of the larger volume of venous blood.

For the hour-long periods of hyperventilation, breathholding measurements of mixed venous tension were made only before and after, but its change after 20 minutes was considered to equal the change of alveolar tension during that time. This was justified by separate observations on two of the subjects in which breathholding measurements were made after 15 or 25 minutes of hyperventilation. The average differences between alveolar and mixed venous tension agreed within 0.5 mm. of mercury whether measured before or after 15, 25 or 60 minutes of hyperventilation. This is, of course, consistent with an increased difference of content of CO_2 between mixed venous and arterial blood at the lower values of CO_2 tension existing during hyperventilation. The mixed venous tension (P_v) was considered to be the best available, but probably inexact, estimate of "tissue" tension.

Partial dissociation slopes of CO_2 were calculated as follows:

$$\text{"Whole body" dissociation slope} = \frac{\triangle \text{ total stores}}{\triangle P_v \text{ (mm. Hg) x weight (kg.)}}$$

$$\text{"Tissue" dissociation slope} = \frac{\triangle \text{ total stores} - \triangle \text{ lung stores} - \triangle \text{ blood stores}}{\triangle P_v \text{ (mm. Hg) x weight (kg.)}}$$

All volumes for stores are in milliliters at 0° C. and 760 mm. of mercury, dry.

Results

The results of a typical hour-long study are presented in figure 2. From a resting volume of 9.3 liters per minute (body temperature, ambient pressure, saturated), ventilation was increased to 13.5 ± 0.1 liters per minute. Following the onset of hyperventilation, oxygen uptake increased abruptly for 5 or more minutes, and then usually decreased to levels slightly greater than the control. For seven hour-long observa-

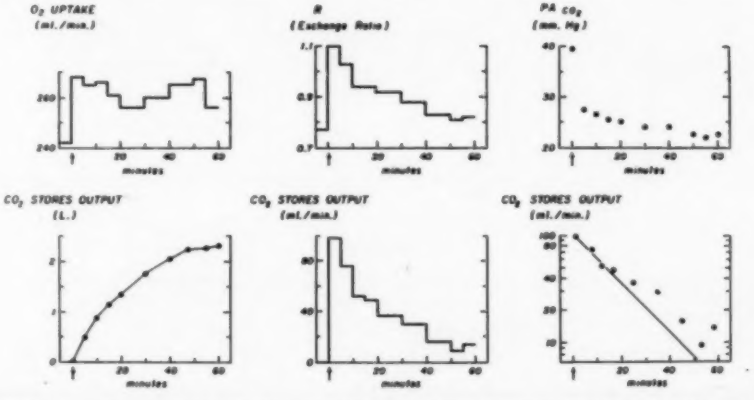

FIGURE 2: Gas exchange during constant voluntary hyperventilation (study WF-3; see text and table 1).

tions on three subjects, the average percentage of the control values for oxygen uptake during the periods of 0 to 10, 20 to 30 and 50 to 60 minutes were 107, 103 and 103 per cent, respectively. The initial increase was attributed in part to accumulation of oxygen stores and in part to the metabolic cost of the increased respiratory work. Assuming the values observed at 15 to 30 minutes to represent only the initial metabolic rate plus the oxygen cost of the increased respiratory work, it was calculated that the average oxygen cost of excess ventilation was 2.6 ml. per liter per minute. This value would be expected to be several times the value of 0.5 to 1.0 ml. per liter required at rest[13], because the increased ventilation was voluntary and because some respiratory work was expended on the apparatus.

The respiratory exchange ratio increased initially and thereafter decreased slowly; in no experiment did it return completely to the resting value. The end-tidal CO_2 tension decreased rapidly for about 5 minutes and thereafter more slowly. The output of stores of CO_2 was initially at a large rate, decreasing thereafter. Elimination continued throughout the period of 1 hour; in the study illustrated, it amounted to 2.3 liters of CO_2.

The semilogarithmic plot shows that the rate of output of stores was not that of a single exponential function but that the rate during the later periods was greater than expected from a continuation of the initial rate. That is, the amount of depletion of stores per minute did not represent a constant fraction of the stores remaining at a particular time.

Observations on one subject (JV) showed that the rate of output of stores varied with the degree of hyperventilation (fig. 3). This would be expected to be more strictly true for increased alveolar ventilation than for total ventilation. The divergently large value for output from 0 to 5 minutes in figure 3 represents a study in which tidal volume and thereby alveolar ventilation were in fact relatively greater than they

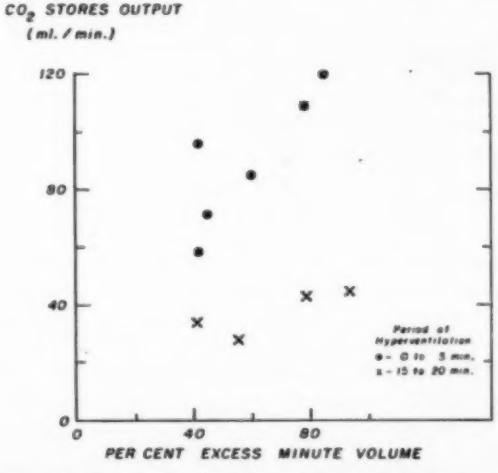

FIGURE 3: Relation between rate of output of stores and extent of hyperventilation (increase of minute volume). Values are those observed during periods of 5 minutes' duration.

were for the other observations plotted. After 15 to 20 minutes, the absolute values of rate of output were less affected by the extent of hyperventilation.

Results for seven hour-long studies are presented in figure 4 and table 1. An increase of ventilation of the order of 50 per cent for 1 hour eliminated from 1.5 to 2.5 liters of CO_2 stores. This represents approximately a reduction of the quantity of CO_2 in the lungs by one third, or 50 ml., and in the blood by one sixth, or 500 ml. The major quantity thus came from other tissues. Despite differences of the total output between individuals, no consistent differences between their calculated dissociation slopes were observed. Similarly, when the change of stores during the first 5 minutes was expressed as milliliters of CO_2 per millimeter decrease of alveolar tension per kilogram, average values of 0.56, 0.56 and 0.61 were obtained for the three subjects. The average "tissue" slope for 1 hour was 1.6 ml./mm./kg., or about 80 per cent of the "total body" slope. More than half the elimination for 1 hour was accomplished within the first 20 minutes. During this period, the loss from the blood represented about 30 per cent of the total, whereas it was only 20 per cent of the total for 60 minutes. The values of dissociation slopes, calculated for the 20-minute period of elimination, were in all instances less than the values for the 60-minute period.

Symptoms of acute hyperventilation, such as dizziness or paresthesia, were not noted, nor did apnea follow the end of hyperventilation for 1 hour. Drowsiness was experienced, as were muscular discomfort from prolonged immobilization and other more vague but unpleasant sensations.

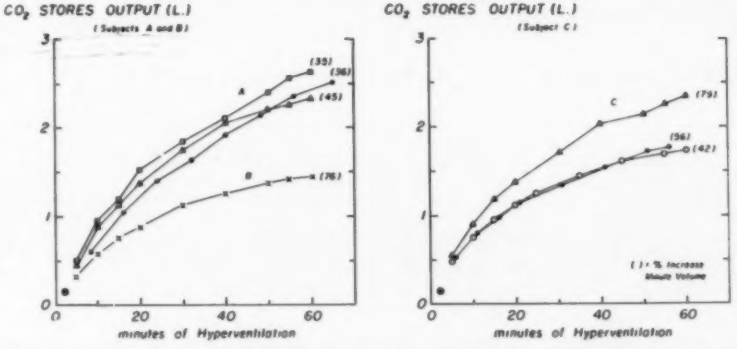

FIGURE 4: Total output of CO_2 stores for three subjects. The concentric circle at 2 minutes is the average value (156 ml.) of seven separate observations in which ventilation was increased an average of 80 per cent.

Comment

The pattern of gas exchange during hyperventilation was in close agreement with that observed by Liljestrand; in his subjects, however, both the degree of hyperventilation and the amount of CO_2 stores eliminated during corresponding periods were greater. With a 300 per cent increase in ventilation for 21 minutes, two of his subjects depleted their stores by about 2.2 liters, whereas our subjects eliminated about 1.2 liters with a 50 per cent increase of ventilation. With constant hyperventilation for 40 minutes, one subject of Liljestrand eliminated about 3.2 liters with a 250 per cent increase of ventilation. It appears that the output of stores may not increase proportionately when ventilation is increased by more than 100 per cent.

TABLE 1—ELIMINATION OF CO_2 STORES DURING HYPERVENTILATION (60 MINUTES AND 20 MINUTES)

Subject	Study	Body weight, kg.	Exchange ratio		Period of hyperventilation, minutes	Increase in minute volume, per cent	Mixed venous CO_2 tension, mm. Hg		Decrease of stores, ml. (standard temperature and pressure, dry)			Dissociation slopes		
			Initial	Terminal 5 to 8 minutes			Initial	Decrease†	Total	Lung	Blood	Whole body Ml./mm.	Whole body Ml./mm./kg.	Tissue, Ml./mm./kg.
JV	1*	78	0.79	0.82	56	56	44.1	8.6	1770	37	262	206	2.64	2.19
JV	2	78	0.88	0.90	61	42	45.8	15.0	1720	42	468	115	1.47	1.03
JV	3	78	0.80	0.87	60	79	45.1	12.8	2345	39	406	183	2.35	1.90
WF	1	82	0.75	0.83	64	36	49.5	11.7	2500	33	361	214	2.60	2.19
WF	2	82	0.78	0.87	60	35	44.2	15.1	2635	44	468	174	2.13	1.72
WF	3*	82	0.77	0.82	60	45	46.3	17.8	2315	59	597	130	1.59	1.14
HH	1	69	0.78	0.80	62	76	46.7	13.8	1470	74	370	107	1.54	1.07
Mean												161	2.05	1.61
JV	1*	78	0.79	0.91	21	56	44.1	13.2	1140	37	419	86	1.11	0.67
JV	2	78	0.88	1.00	20	42	45.8	13.8	1120	38	431	81	1.04	0.60
JV	3	78	0.80	0.96	20	79	45.1	11.1	1390	37	343	125	1.56	1.13
WF	1	82	0.75	0.92	20	36	49.5	8.6	1225	24	256	142	1.73	1.34
WF	2	82	0.78	1.03	20	35	44.2	14.0	1540	42	466	110	1.34	0.90
WF	3*	82	0.77	0.94	20	45	46.3	14.6	1375	49	479	94	1.15	0.71
HH	1	69	0.78	0.87	20	76	46.7	11.0	880	59	287	80	1.16	0.70
Mean												103	1.30	0.86

*After overnight fast.

†Estimated by breathholding after the 60-minute period, and by change of alveolar tension for the 20-minute period.

Farhi and Rahn, in their informative analysis of gas stores, concluded that elimination of the readily available stores of CO_2 in anesthetized dogs proceeded in an exponential manner, with a half time of 4 minutes. However, our results, as well as those of Liljestrand, in man indicate a more complex and prolonged process. Even if one determines a minimal half time from the initial and terminal rates of output, it is at least about 15 minutes. Also, Shaw and Messer's[8] data on cats are probably not consistent with a half time as small as 4 minutes. It appears unlikely that all of the stores would exchange in a manner describable by a single exponential function, as this implies a single bodily pool of CO_2. There are probably multiple sites or pools with varying rates of exchange. The results presented here demonstrate the different rates of exchange of alveolar gas, blood and "tissues." The much larger dissociation slopes obtained from prolonged observations in animals (table 2) demonstrate the existence of CO_2 in tissues, including bone, that is very slowly exchangeable.

The change of tension of mixed venous blood has been used to estimate that of the "tissues." The extent to which this is justifiable in an unsteady state is uncertain. In three studies of Liljestrand, hyperventilation was maintained for about 20 minutes and then reduced for about 30 minutes to approach a new steady state; in these studies, there is no consistent difference in dissociation slope whether it is calculated from the stores output and change of alveolar tension at 20 minutes, when the exchange ratio was still increased, or at 50 minutes, when the ratio had returned to control values.

Our values for the "whole body" dissociation slope, averaging about 2 ml./mm./kg., are similar to those previously obtained in man and animals by observations of similar duration (table 2) and pertain to the extent of equilibration obtainable in 1 to 2 hours. With more nearly complete equilibration over periods of many hours or days,[14] much larger values are obtained.[9]

The dissociation slopes calculated from different observations were of similar order but did not agree closely for an individual, whether the change in mixed venous tension or the directly measured change in alveolar tension was used in calculation. Some of the variability may have been caused by changes of metabolic rate during the procedure. The methods used for calculation of change of stores, assuming a constant metabolic R.Q., are apparently justifiable when total metabolic rate is constant during the control and the hyperventilation periods. However, we have some reservations about their exactitude in the situation when a simultaneous increase in metabolic rate occurs during the period of elimination of stores caused by the increased rate of ventilation. It was also noted that in some studies in which the uptake of oxygen increased during the latter part, probably from muscular activity[5] associated with restlessness, the alveolar CO_2 tension remained essentially constant throughout the later periods. Presumably, there was also an increasing metabolic production of CO_2, which offset the continued gradual decrease of alveolar tension that would be excepted from elimination of stores alone. However, the failure of elimination to proceed at a single expontial rate was observed whether or not the rate of oxygen uptake increased.

The quantitative aspects of elimination of stores of CO_2 bear on the problems of therapeutic management of patients with chronic retention of CO_2. An estimate of the quantity of retained CO_2 may be made from the finding that rats exposed to 10 per cent CO_2 for periods up to 4 weeks showed an average increase in total body CO_2 of about 20 per cent.[9] This probably would represent more than 20 liters in adult humans, which is large relative to the 2 liters that were eliminated by hyperventilation for 1 hour. It is uncertain whether similar elimination would be achieved by mechanical hyperventilation of patients with pulmonary emphysema and CO_2 retention.

The arterial CO_2 tension is often used clinically to assess the level of CO_2 in the body. It should be recognized that such an interpretation, if strict, implies the existence of a steady state. The arterial tension, neglecting venoarterial shunts, reflects most directly the alveolar tension, which may be altered much more rapidly than that of the tissues. Following a maintained change of the ratio of alveolar ventilation to metabolic production, as in these studies, prolonged periods are required to approach the new equilibrium. However, the physiologic mechanisms that regulate breathing normally act to maintain constancy of this ratio, thus tending to minimize the extent

TABLE 2—CO_2 DISSOCIATION SLOPE OF THE WHOLE BODY

Ref.	Species	Equilibration period	Slope, ml./mm./kg.
(2)	Man	<60 min.	2.0 - 2.5
(*)	Man	60 min.	1.5 - 2.6
(1)	Dogs	40 - 50 min.	1.5
(8)	Cats	45 - 140 min.	1.8
(5)	Cats	3 - 5 hours	>10
(9)	Rats	Days	11.6

*This report.

of departures from the steady state. In view of the many factors affecting the production, storage and elimination of CO_2 that are encountered in patients with CO_2 retention, it is not clear to what extent the theoretically necessary steady state can or must be achieved to permit the proper evaluation of tissue levels of CO_2 from those measured in arterial blood. However, it has been observed that coma may persist during recovery from prolonged CO_2 narcosis even after the CO_2 tension in the arterial blood has been reduced to levels not ordinarily associated with alterations of consciousness.[15]

SUMMARY

Adjustments of body stores of carbon dioxide were studied during voluntary hyperventilation for 1 hour at a constant rate by trained subjects. Healthy men eliminated from their stores an average of 161 ml. of CO_2 per mm. of mercury decrease in mixed venous tension, corresponding to a partial dissociation slope for body stores of 2.05 ml./mm./kg. Increasing the respiratory minute volume by about 50 per cent for 1 hour produced elimination of 1.5 to 2.5 liters of CO_2 in excess of the metabolic production, which is a small part of the 100 or more liters estimated to be present in the body. The elimination of stores during a period of 1 hour did not appear to proceed at a single exponential rate, which is consistent with the presence of multiple storage sites or pools that exchange at different rates. In unsteady states, such as may exist during development of or recovery from CO_2 retention and narcosis, the arterial CO_2 tension may not adequately reflect the tissue levels.

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RESUMEN

Se estudiaron los ajustes de la reserva de dióxido de carbono en el cuerpo por medio de la hiperventilación voluntaria por una hora con ritmo constante en los sujetos. Los hombres sanos eliminan de sus reservas un término medio de 161 ml. de CO_2 por mm. de decrecimiento de mercurio en tensión venosa mixta, correspondiendo a una disociación parcial en decrecimiento de sererva corporal de 2.05 ml/mm./Kg. Aumentando el volumen-minuto aproximadamente el 50 por ciento por una hora produjo eliminación de 1.5 a 2.5 litros de CO_2 en excesos de la producción metabólica que es una pequeñe parte de los 100 o más litros calculados como presentes en el cuerpo.

La eliminación de reservas durante el período de una hora no parece seguir en una proporción exponente, lo que está de acuerdo con el hecho de que existen múltiples focos de reserva o lagunas de reserva que sufren el cambio con ritmos diferentes.

En las condiciones no estables tales como la que puede existir durante el desarrollo o en la recuperación de retención de CO_2 después de narcosis, la tensión arterial de CO_2 puede no reflejar adecuadamente los niveles en los tejidos.

RESUMÉ

Les auteurs ont étudié les adjustements des réserves de l'organisme en gaz carbonique pendant une hyperventilation volontaire d'une heure à taux constant sur des sujets entrainés. Les hommes en bonne santé éeliminèrent de leurs réserves une moyenne de 161 mml. de gaz carbonique par mm. de chute de mercure sur la tension veineuse, ce qui correspond à une dissociation partielle des réserves de 2,05 mml. par mm. de mercure et par kilogramme. L'augmentation du volume respiratoire minute de 50% en une heure produisit une élimination de 1,5 à 2,5 litres de gaz carbonique en excès dans le métabolisme, ce qui est une petite partie des cent et quelques litres qu'on estime présents dans le corps. L'élimination de réserves durant une période d'une heure ne sembla pas procéder d'un simple taux exponentiel compatible avec la présence de points de stockage ou de réserves qui se modifient selon la variation des taux. Dans les états instables, tels qu'il peut en exister pendant le développement ou la cessation de la rétention de gaz carbonique dans l'anesthésie, la tension artérielle en gaz carbonique peut ne pas refléter exactment el taux des tissues.

ZUSAMMENFASSUNG

Es wurde der Ausleich der CO_2-Vorräte des Körpers während freiwilliger Hyperventilation von einer Stunde Dauer mit konstanter Zahl bei trainierten Personen geprüft. Gesunde Männer schieden von ihren Reserven durchschnittlich 161 ccm CO_2 pro Millimeter Quecksilberabfall aus, bei gemischter venöser Spannung; das entsprach einem teilweisen Dissoziaitions-Abfall für Körperreserven von 2,05 ccm/mm/kg. Eine Zunahme des Atemminutenvolumens von ungefähr 50% eine Stunde lang führte zu einer Ausscheidung von 1,5 bis 2,5 Litern von CO_2 aus dem Überschuss des intermediären Stoffwechsels; dies ist ein kleiner Teil der 100 oder mehr Liter, auf die die im Körper vorhandenen Vorräte geschätzt werden. Die Ausschüttung der Reserven während der Zeit von einer Stunde schien nicht nach einer bestimmten Exponentialzahl bu erfolgen, die auf das Vorliegen multipler Reservoire schliessen lässt, die in verschiedenem Tempo ausgewechselt werden. Bei gestörtem Gleichgewicht wie es

vorkommt bei der Entstehung oder Rückbildung von CO_2 Retensionen und Narkose, kann es geschehen, dassdie arterielle CO_2-Spannung kein adäquates Spiegelbild der Werte für das Gewebe darstellt.

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Relationship of Height to Lung Volume in Healthy Men*

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The accurate definition of physiologic normality in man is a prerequisite to quantitation of disease. It has long been known that the total lung volume or a subdivision thereof of a person has limited significance as an isolated measurement unless it can be compared to a normal value. Although the ranges of normality of the various subdivisions, when expressed as a percentage of the normal total capacity, have been established, one still must know what the total capacity should be under normal conditions before actual values of it and its subdivisions can be evaluated in terms of being normal or abnormal. Ever since Hutchinson[1] first reported his extensive study of the vital capacity of man, many attempts have been made to define the correlations between vital capacity (and later, total capacity) and various physical measurements in the hope that it would be possible to predict accurately the normal lung volumes from certain physical measurements. Hutchinson correlated vital capacity with standing body height. In addition, stem height, weight, surface area, circumference and volume of the thorax, radiologic lung area or volume, age or any combination of these measurements has been utilized in predicting lung volues.[2-21] Most attempts have been made at trying to describe a linear correlation between body build and lung volume. Good correlations pertained over only limited ranges. To overcome this, formulas utilizing multiple linear correlations have been derived.

Kelly,[22] in a study of vital capacity of boys and girls, first identified the relationship between vital capacity and the cube of height. Bateman[23] later expressed the relationship of the total lung volume and its subdivisions to the third power of the body height of adults of average stature. Subsequently, Morse and associates,[24] Helliesen and co-workers,[25] and Engström and associates[26] described this relationship in boys and girls.

It is the purpose of this study to determine if this relationship still pertains when the height levels are extended beyond the ranges heretofore reported.

Methods

Measurements of vital capacity and total lung capacity were made on 39 healthy male physicians and laboratory workers ranging from 21 to 44 years of age. Older persons were not included in order to avoid the well-known effects of age on vital capacity. In addition to men of average height, men were selected who were unusually tall, including 15 who

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TABLE—LUNG VOLUMES AND HEIGHT OF MEN AND BOYS

Authors	Mean age in years (range)	Mean height in cm. (range)	Ratio of lung volume to cube of height (liters/M³) Total capacity Mean; S.D.; S.E. of mean	N†	Vital capacity Mean; S.D.; S.E. of mean	N†	Ratio of observed to predicted values* Total capacity Mean; S.E. of mean; coefficient of variation (%)	Vital capacity Mean; S.E. of mean; coefficient of variation (%)
Bateman-Birath	28	175.9	1.177		0.896			
	(18-39)	(164-186)	0.141	28	—	28	—	—
			0.027		—			
Helliesen	11.0	147.6	1.138		0.872		.964	.968
	(5-17)	(110-184)	0.147	50	0.117	52	.018	.018
			0.021		0.016		13.0	13.5
This report								
Total capacity	31	180.4	1.216		0.908		1.031	1.009
	(21-44)	(164-198)	0.129	39	0.103	76	.018	.013
Vital capacity	31	184.3	0.021		0.012		10.7	11.0
	(22-41)	(164-206)						

*Predicted as VC=0.9 Ht² and TC=1.18 Ht² (VC and TC in liters; Ht in meters).
†N is number of subjects.

were 6 feet (183 cm.) or more in height. Determinations of vital capacity only were done on 37 additional men, including 10 professional basketball players. In these last 10 men, vital capacity was measured with the subjects standing; otherwise, measurements were made in the seated position and the men were not fasting.

The total capacity was measured by adding the vital capacity, obtained by use of a Benedict-Roth type of spirometer, to the residual volume. The latter was determined by a modification, previously described,[27] of Darling's open-circuit, nitrogen-elimination method. All volumes are expressed at BTPS (body temperature, ambient pressure, saturated).

Results

The results are listed in the accompanying table, along with Bateman's[23,28] compilation of his and Birath's[29] data on young men, and

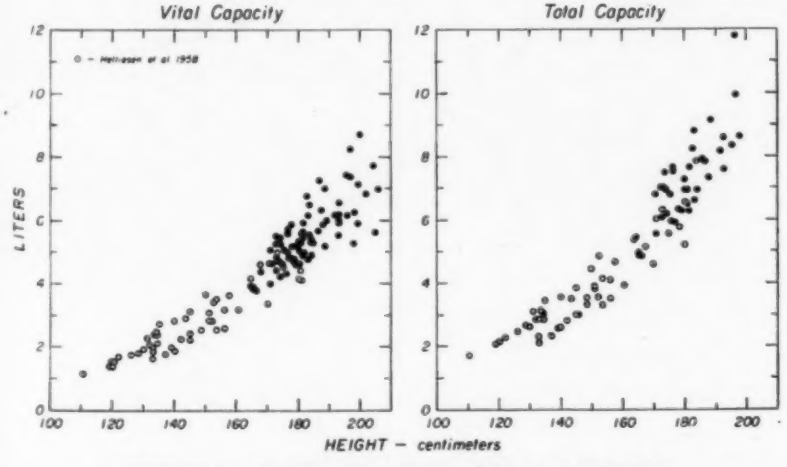

FIGURE 1: Relationship of lung volumes to body height.

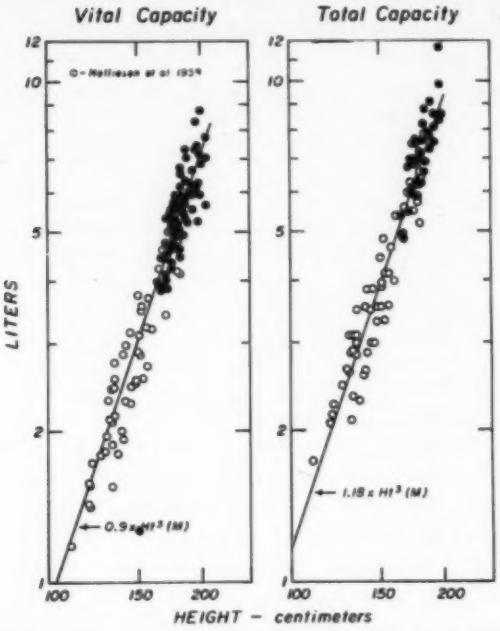

FIGURE 2: Relationship of lung volumes to body height. Same data as in figure 1, but on a double logarithmic scale.

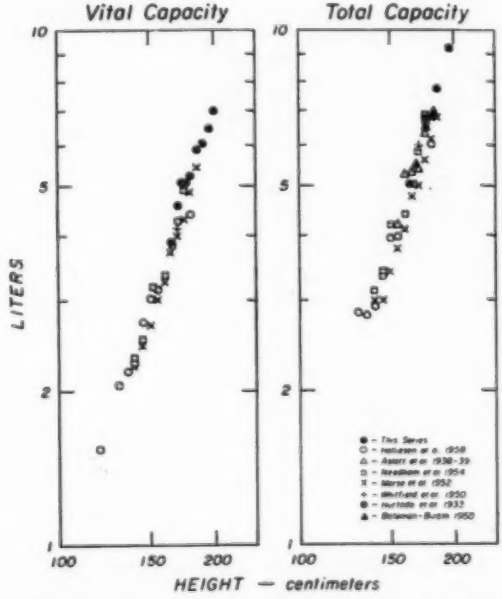

FIGURE 3: Relationship of lung volumes and body height. Comparison of mean values from a number of sources.

measurements on boys by Helliesen's group.[25] The latter data also are plotted with the results of this study in figure 1. It is evident that lung volume is not a linear function of height. Figure 2 shows the same data on a double logarithmic scale. The straight lines represent the mean values calculated by Bateman for men of heights ranging from 164 to 186 cm. The same relationship evidently applies almost equally well from about 110 to 205 cm. of height. Data on male subjects reported previously by others are summarized in figure 3. We have calculated the average volumes for each range of height of 5 cm.; all were corrected to BTPS and for the effect of the recumbent position when necessary. Since the study of Aslett's group[15] included men up to 63 years of age, their data on vital capacity were omitted and only data for total lung volume were used.

It is evident that our data for men of average height coincide with those of previous studies and that the cube of height also applies to lung volumes of men taller than 6 feet (183 cm.).

We have calculated the variation of our measurements and those of Helliesen and co-workers from values estimated from Bateman's prediction formula (see table). The mean values differ by only a few per cent, and the coefficients of variation of 10 to 13 per cent are similar to Bateman's values.

Figure 4 presents our average values for each 5-cm. segment of height, plotted on an arithmetic scale. This permits a comparison with the values predicted by several of the more widely used and recent formulas that predict vital capacity as a linear function of height.[1,5,30,31] When age was also a variable in the formula, the average age of our subjects, namely 31 years, was used. It is apparent that even the best linear formula predicts values that are too small as height increases above the average and too large in the shorter height range of the

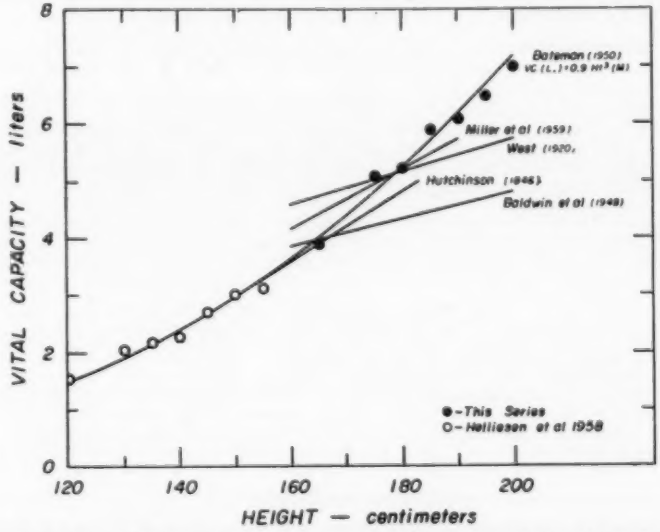

FIGURE 4: Measured vital capacities and various prediction formulas.

pediatric age. It should be stated that all these formulas were designed for adults and were not considered as necessarily applying to children.

Comment

Of the various measurements of body build, height generally has been found to be the single measurement with which lung volumes can be correlated best. Previous studies describing lung volumes as a linear function of height dealt for the most part with persons of a limited height range; over such limited ranges, the correlation may be satisfactory. However, the correlation is not satisfactory when the height range is extended.

It appears reasonable that a better correlation should exist between lung volumes and the third power of height than with the first power of height, since the body is three-dimensional. This has been pointed out several times in the literature, but its use has not been widely adopted. Although the relationship between lung volumes and the cube of height is similar for a range between 120 and 206 cm., there are data to indicate that equations having the same coefficients or exponent or both may not apply to newborns and infants. Anthropometric studies show that the ratio of actual body volume to the cube of body height in infants is almost twice that in adults,[22] which is a reflection of the relatively large trunk and head of the newborn. Other anatomic studies show that the ventilatory portions of the lung lag behind in development, and the adult ratio of ventilatory to nonventilatory tissue is established at about 3 years.[33,34] The functional residual capacity of newborns has been determined by Berglund and Karlberg;[35] on the basis of the relationship to metabolic rate, it was considerably smaller than in adults. If the functional residual capacity (liters) equalled 0.5 times the cube of the height (meters), it would be 62.5 ml. in an infant 50 cm. in length. This is less than the value of about 95 ml. that was observed for a 3.5-kg. infant.

The older literature stated that athletes and people indulging in strenuous physical labor tend to have larger vital capacities[2]. However, other studies[36,37] do not support this concept, while one study[38] indicated that the vital capacity increases after much skin diving. For the 10 tall (193 to 206 cm.) professional athletes in our study, the mean ratio of measured to predicted vital capacity was 0.94, using the same formula as for nonathletes (see table). One well-proportioned, 28-year-old athlete, 200 cm. tall and weighing 105 kg., had a vital capacity of 8.76 liters, which to our knowledge is the largest recorded value in the literature.

SUMMARY

Measurements of vital capacity and total lung capacity were made on healthy men of heights up to 206 cm. (81 inches), extending previous measurements on boys and men of average height. In the range between 120 and 206 cm. of height, lung volumes are closely related to the third power of height, as shown by others. The prediction formula of Bateman, relating volume to the cube of height, is applicable over greater ranges of height than are other linear equations in current clinical use for estimating the normal lung volumes from height.

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RESUMEN

Se llevaron a cabo las medidas de la capacidad vital y de la capacidad pulmonar total de hombres de estatura hast de 206 cms. (81 pulgdas) además de las medidas de jóvenes y hombres adultos de estatura media. Entre las estaturas de 120 a 206 cms., los volúmenes están en relación estrecha con la tercera potencia de la altura como otros lo han mostrado.

La fórmula para la predicción de Bateman relacionado el volumen al cabo de la altura es aplicable a las estaturs myores más que otrs ecuaciones lineales en el uso clínico corriente para valuar los volúmeues normales del pulmón de acuerdo con la estatura.

RESUMÉ

Des mésures de la capacité vitale et de la capacité respiratoire totale furent faites sur des individus sains dont la taille allait jusqu'à 2 m.06. Il s'agit donc d'une extension des mesures antérieures qui portaient sur des garçons et des hommes de taille moyenne. Dans la limite comprise entr Im.20 t 2m.06, les volumes respiratoires sont étroitement liés au tiers de la taille, comme d'autres l'ont montré. La mormule de Bateman, liant le volume respiratoire au cube de la hauteur, est applicable sur de plus grandes échelles de taille que ne le sont les équations linéaires dans l'emploi clinique courant pour évaluer les volumes respiratoires normaux d'après la taille.

ZUSAMMENFASSUNG

Es wurden Messungen der Vitalkapazität und des gesamten Lungenvolumen vorgenommen bei gesunden Männern mit einer Körpergrösse bis zu 206 cm in Erweite-

rung vorausgegangener Untersuchungen an Knaben und Männern mit durchschnittlicher Körpergrösse. Bei Werten zwischen 120 und 206 cm Körpergrosse liegen, wie auch von andered Seite gezeigt worden ist, die Lungenvoluminas dicht bei der dritten Potenz der Körperbrösse. Die Sollwertsbestimmungsformel von Batemann, die das Volumen in Beziehung setzen zur Kubikzahl der Körperbrösse, lassen sich für einen grösseren Bereich von Körpergrössen verwenden als andere lineare Gleichungen, die meist bei klinischem Gebrauch verwandt werden zur Bestimmung der normalen Lungenvolumina aus der Körpergrösse.

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Pleural Fluid Glucose with Special Reference to its Concentration in Rheumatoid Pleurisy with Effusion*

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Is measurement of the concentration of glucose (reducing substances) in pleural fluid of any clinical value? A partial review of the literature did not answer this question. Some reports[1-6] suggest that a low concentration of glucose is of value in differentiating various causes of pleural effusion. Others[7-10] present evidence to the contrary. This confusion led us to carry out a study.

Method and Results

For a period of several months in 1957 and 1958 the concentration of glucose was measured in all specimens of pleural fluid that were sent to the chemistry laboratory. The analytic method most used was that of Folin and Wu,[11] in which trungstic acid filtrate is heated with an alkaline copper solution. However, a number of the more recent analyses (since December 1, 1958) have been done by the Autoanalyzer method as modified for use in our laboratory.[12] This procedure excludes many of the nonglucose reducing substances that usually are present in tungstic acid filtrates, and the values obtained approximate those for so-called true glucose.

It was not practical routinely to withhold breakfast before the pleural fluid was aspirated. Neither were we able to take samples of blood for the glucose tests simultaneously with the aspiration.

The concentrations of glucose were correlated with the clinical diagnoses, as shown in table 1.

TABLE 1 — RELATION BETWEEN DIAGNOSIS AND CONCENTRATION OF GLUCOSE IN PLEURAL EFFUSION

Diagnosis	Number of fluids in which glucose per 100 ml. was			
	<30 mg.	30-60 mg.	61-120 mg.	>120 mg.
Malignancy with malignant cells in pleural fluid			17	12
Malignancy without malignant cells in pleural fluid		1	6	4
Congestive heart failure			1	6
Pulmonary infarct		1	3	
Rheumatoid arthritis	4			
Miscellaneous*		1	4	1
Indeterminate	1	1	5	4

*Pneumonia, mediastinitis, thoracotomy, automobile accident, subphrenic abscess, and acute pancreatitis.

To our surprise we encountered three patients (one of them with bilateral effusion) who had extremely low concentrations of glucose in the pleural fluid. Each of these patients had active rheumatoid ar-

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thritis. As no other cause for the pleural effusion could be detected, despite thorough study, we concluded that these patients had rheumatoid pleurisy with effusion. In recent months we have encountered three more patients having active rheumatoid arthritis with pleural effusions apparently due to the rheumatoid process.

Certain data from these six cases are given in table 2. In each case the fluid was described as yellow, green, or greenish-yellow, and cloudy or turbid. Each sample of fluid was examined for malignant cells, but none were found. Each was cultured for acid-fast bacilli and for fungi, but all cultures were negative. A more detailed report on these six cases is being prepared.

TABLE 2 — DATA ON RHEUMATOID PLEURAL EFFUSIONS

Case	Age and sex	Side	Date	Amount aspirated, ml.	Protein, gm./100 ml.	Fat, mg./100 ml.	Glucose, mg./100 ml.	Blood glucose, mg./100 ml.	Patient fasting
1	44M	L	8-26-57	1100	3.4		< 5		No
		R	9-7-57	900	3.7		6		No
2	39M	L	11-29-57	350	6.7	648	5		No
3	55M	L	4-7-58	500	5.7		< 5		Yes
4	63M	L	2-12-59	1050	5.4	521	10		No
5	63M	R	6-8-59	1050	4.9		10	52	Yes
		R	6-11-59	980	5.1	492	< 5	56	Yes
6	52M	R	6-9-59	150	4.3		17	82	No
		R	6-19-59	250	6.0	336	< 5	60	Yes
		L	6-26-59	500	5.3	382	< 5	58	Yes
		R	6-29-59	90			< 5	118	No
		L	6-29-59	15			< 5	118	No
		R	7-3-59	350	5.1		< 5	112	No

Comment

Disappointingly, no patients having tuberculous pleurisy with effusion were encountered during the period of study. Consequently we can neither confirm nor deny the reports that the concentration of glucose in pleural fluid is usually low when the effusion is due to tuberculosis. We can confirm the reports that the concentration of glucose is not low in certain other conditions such as malignancy, congestive heart failure, pulmonary infarction, and miscellaneous injuries to and inflammations of the pleura.

Our study did not answer our question. However, it did reveal that tuberculosis is not the only cause of a decreased concentration of glucose in pleural fluid and it called our attention to the condition "rheumatoid pleurisy with effusion." Emerson[13] reported a similar group of cases in 1956 but did not mention the concentration of glucose in the fluids aspirated from his patients. Our review of the literature on pleural-fluid glucose revealed only one instance in which it was associated with any rheumatic condition: Courtois and Vanroux[4] mentioned a patient having a febrile illness with rheumatism and a pleural effusion that was found to contain 82 mg. of glucose per 100 ml. of fluid on one examination and 93 mg. per 100 ml. on another examination 18 days later.

How the concentration of glucose in the pleural fluid is controlled is not completely clear. Durieu[5] has preesnted the best explanation that we have seen. He pointed out that the concentration of glucose in the pleural fluid depends on its concentration in the blood, the ease with which it diffuses into the pleural fluid, and the rate of glycolysis in the fluid. The rate of diffusion is affected not only by the disease causing the effusion but also by the volume of fluid. Large volumes collapse the lung, decreasing the pulmonary circulation, and thus interfere with the diffusion of glucose into the pleural fluid. The rate of glycolysis has some relation to the leukocyte count, but Durieu indicates that there are other contributing factors.

These ideas do not explain to us why our patients having rheumatoid pleurisy with effusion should have such low concentrations of glucose in the pleural fluid. The volumes of fluid were not large enough to collapse the lungs completely and cut off the pulmonary blood flow. Pleural biopsies in two of our cases revealed nothing that could be interpreted as a barrier to the diffusion of glucose. Unfortunately the leu-

kocytes were not counted in any of the fluids, but none of them wer purulent. We believe that further study is needed to explain the remarkably low concentration of glucose in rheumatoid pleural effusions.

Incidentally, Ropes and Bauer[14] have reported that in rheumatoid arthritis the concentration of glucose in the joint fluid may be significantly lower than the concentration of glucose in the blood, and in some cases the joint fluid may contain no glucose at all.

To return to our original question, we must conclude that the measurement of the concentration of glucose in pleural fluid is not of great clinical value, as neither low nor high concentrations are diagnostic of any specific disease. However, it is obvious that the careful correlation of the concentration of glucose with other data would in some cases be of help in suggesting the correct diagnosis or in avoiding an incorrect diagnosis.

SUMMARY

The concentration of glucose in pleural fluids that are due to malignant lesions, congestive heart failure, pulmonary infarction, and miscellaneous inflammatory and traumatic conditions was found to be more than 60 mg. per 100 ml. of fluid in 54 of 57 fluids, and between 30 and 60 mg. per 100 ml. in the remaining three. In contrast, six patients having rheumatoid arthritis with rheumatoid pleurisy and effusion were found to have pleural-fluid glucose concentrations varying from less than 5 to 17 mg. per 100 ml.

As tuberculosis also has been reported to cause very low concentrations of glucose in pleural fluid, we concluded that the measurement of the concentration of glucose in pleural fluid was of only slight value in the differential diagnosis of the diseases causing pleurisy with effusion.

RESUMEN

La concentración de glucosa en el líquido pleural que se debe a lesiones malignas, a insuficiencia cardiaca congestiva, infarto pulmonar y diversas enfermedades inflamatorias y traumáticas, se ha encontrado que sobrepasa los 60 mgrs. por 100 ml. de líquido en 54 de 57 líquidos estudiosos y fué entre 30 y 60 mgrs. en los tres restantes. Por el contrario, seis enfermos de artritis reumatoide con pleuresía reumatoide y derrame, se encontró que tenían concentraciones de glucosa en el líquido pleural variando de 5 a 17 mgrs. por 100 ml.

Como la tuberculosis se ha relatado que causa muy bajo concentración de glucosa en el líquido pleural, concluímos que la medida de la concentración de glucosa en el líquido pleural tiene poco valor para el diagnóstico diferencial de las enfermedades que causan ese derrame pleural.

RESUMÉ

Les auteurs ont constaté que la concentration de glucose dans les liquides pleuraux dus à des lésions malignes, à une atteinte cardiaque, à un infarctus pulmonaire et à divers états inflammatoires et traumatiques, était de plus de 60 mmg. par litre de liquide dans 54 des 57 liquides examinés, et entre 30 et 60 mmg. pour un litre pour les trois autres. En contraste six malades atteints de rhumatisme articulaire avec épanchement pleural présentèrent des concentrations de glucose dans le liquide variant de moins de 5 à 17 mmg. par litre.

Comme il a été constaté que la tuberculose est également susceptible de donner lieu à de très basses concentrations de glucose dans le liquide pleural, les auteurs estiment que la mesure de la concentration du glucose dans le liquide pleural est de faible valeur dans le diagnostic différentiel des effections qui peuvent provoquer une pleurésie avec épanchement.

ZUSAMMENFASSUNG

Es ergab sich eine Glucose-Konzentration in pleuralen Ergüssen infolge maligner Affektionen, Herzinsuffizienz, Lungeninfarkt und verschiedener entzündlicher und traumatischer Ursachen von mehr als 60 mg% bei 54 von 57 Fällen, und zwischen 30 und 60 mg% bei den übrigen 3 Fällen. Im Gegensatz dazu liessen sich bei 6 Kranken mit rheumatischer Arthritis und rheumatischer Pleuritis mit Erguss Glucose-Konzentrationen in der Pleuraflüssigkeit nachweisen, die zwischen weniger als 5 und 17 mg% lagen.

Dan von der Tuberkulose berichtet wird, dass auch sie zu sehr niedrigen Glucose-Konzentrationen in der Pleuraflüssigkeit führt, zogen wir den Schluss, dass die Bestimmung der Glucose-Konzentration in Pleuraergüssen nur von geringem Wert ist bei der Differential-diagnose derjenigen Krankheiten, die eine Pleuritis mit Erguss bedingen.

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Primary Pulmonary Histiocytosis X*

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During the past 40 years, three previously unrecognized disorders of the reticuloendothelial system have been described: Letterer-Siwe's disease,[1] Hand-Schüller-Christian's disease,[2-4] and eosinophilic granuloma.[5,6] Due largely to the influence of Lichtenstein,[7] the opinion now prevails that these three disorders are fundamentally related. They differ from one another mainly in terms of patient's age at onset and rapidity of progression. The microscopic pathologic feature characteristic of each of these conditions is the infiltration of tissue by large numbers of histiocytes. The etiology in each instance is unknown. For those reasons Lichtenstein proposed the term "histiocytosis X" to encompass all three disorders.[7]

It has been known for some time that histiocytosis X may have its origin in an organ or organic system other than the lung, and that it may involve the lungs later during the course of dissemination.[8] More recently a number of cases have been reported in which the disease apparently originated in the lung.[9-19] Various terms have been used to designate this form of histiocytosis X, including eosinophilic granuloma of the lung,[9-12,16-20] primary pulmonary eosinophilic granuloma,[14] and pulmonary histiocytosis X.[15] The term "primary pulmonary histiocytosis X" is perhaps more appropriate, since it refers to both the site of origin and the basic pathology of the disease process. In a few of the cases of primary pulmonary histiocytosis X reported in the literature, diabetes insipidus occurred as a complicating condition.[11,15] However, no case has yet been reported in which histiocytosis X involved the lungs primarily and then later became widely disseminated with evidence of osseous and other visceral involvement.

In an effort to learn more of the natural history and influence of various forms of treatment on this disease, the experience with primary pulmonary histiocytosis X at the Mayo Clinic was reviewed. The present paper summarizes this experience and makes certain comparisons with the experiences of others already recorded in the literature. In addition, future avenues of study of patients with primary pulmonary histiocytosis X are suggested.

Materials and Methods

Between July 1953 and July 1959, nine patients with proved histiocytosis X of the lungs were seen at the clinic. In each of these patients the anatomic diagnosis was established by means of biopsy or necropsy. The clinical records, microscopic pathologic specimens, and roentgenograms of these nine patients were reviewed. Follow-up questionnaires were sent to all patients who were still living.

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Among the nine patients, two had disseminated histiocytosis. It was apparent that in each of these patients the lungs had become involved secondarily, the disease having originated in another organ. Neither of these cases will be discussed further in the present report. All of the remaining seven patients appeared to have the primary pulmonary form of histiocytosis X. These seven patients will now be considered from the standpoint of the clinical course, treatment, and prognosis of their disease (table 1). A review of the literature disclosed 21 additional cases in which a diagnosis of primary pulmonary histiocytosis X had apparently been well established (table 2).

Clinical Data

Age, Sex and Race — The ages of the seven patients seen at the clinic ranged from 17 to 60 years, with a median of 39 years. Three patients were in the fourth decade of life. Six of the seven patients were males. All seven patients were Caucasian.

The ages of the 21 patients whose cases were reported in the literature varied from 15 to 57 years, with a median of 27 years. All but two patients were males, and all but one were Caucasian.

These observations suggest that primary pulmonary histiocytosis X rarely occurs in women, and such may well be the case. However, the extreme predominance of men in the cases reported in the literature should be interpreted with some caution, because this group is weighted rather heavily with patients who were in armed forces hospitals when studied, and all of the patients were men.

Symptoms — Primary pulmonary histiocytosis X tends to be characterized throughout its course by relatively minor symptoms. A mild dry or slightly productive cough was present in all seven patients in the clinic series. Cough was a symptom in 16 of the 21 reported cases

TABLE 1 — PRIMARY PULMONARY HISTIOCYTOSIS X
(MAYO CLINIC SERIES)

Case number	Age (yr.) and sex	Complications	Time: onset to diagnosis (months)	Follow-up after diagnosis (months)	Status of patient and x-ray findings at end of follow-up	
					Clinical Status	Thoracic roentgenogram
1	39 M	Pneumothorax (four times)	12	38	Moderate pulmonary insufficiency	
2	60 M		1	14	Asymptomatic	Considerable clearing
3	50 M		2	12	Asymptomatic	Moderate clearing
4	39 F		14	1.5	Mild pulmonary insufficiency	No change
5	27 M	Diabetes insipidus	11	10	No pulmonary symptoms	Moderate clearing
6	17 M	Pneumothorax (four times); diabetes insipidus	12	32	No pulmonary symptoms	Increased fibrosis
7	31 M	Pneumothorax (once); diabetes insipidus; cor pulmonale	108	1.5	Died 6 weeks after diagnosis	

TABLE 2 — PRIMARY PULMONARY HISTIOCYTOSIS X (CASES COLLECTED FROM THE LITERATURE)

Case number	Age (yr.) and sex	Complications	Time: onset to diagnosis (months)	Follow-up period after diagnosis (months)	Status of patient and x-ray findings at end of follow-up	
					Clinical status	Thoracic roentgenogram
8[9]	32 M		8	16		Considerable clearing
9	24 M		10	24		Granulomas still present; fibrosis unchanged
10[10]	35 M		2	3.5	Asymptomatic	"Clearing of lung fields"
11	23 M		8	12	Asymptomatic	
12[11]	32 M	Pneumothorax; diabetes insipidus	36	12	Unchanged	No change
13[12]	15 M		10	10	Asymptomatic	Slight clearing
14[13]	33 M	Pneumothorax (twice)			Died of pneumothorax 3 weeks after onset of symptoms	
15	35 M	Cor pulmonale				
16[14]	26 M		8	18		Increased fibrosis; decreased nodularity
17	23 M		7	4	Asymptomatic	Nodules clearing; fibrosis unchanged
18	27 M		1	14	Asymptomatic	No change
19	35 M		"Many"	10	Asymptomatic	No change
20	52 M		12	2	Asymptomatic	No change
21[15]	22 M	Diabetes insipidus; pneumothorax (many)	12	15	No change	No change
22[16]	20 M		9	19	Asymptomatic	No change
23	23 M	Pneumothorax (twice)	35	16	Improved	No change
24	24 M	Pneumothorax	5	6	Asymptomatic	Slight clearing
25[17]	42 M (Negro)		6	7	Asymptomatic	Considerable clearing
26[18]	21 F		12	9	Asymptomatic	Considerable clearing
27[19]	30 F		4	14	Asymptomatic	Moderate clearing
28	57 M		30	9	Moderate pulmonary insufficiency	Moderate clearing

carried out was a 17-year-old boy whose disease was less extensive and of shorter duration than in the other two patients. No abnormalities of pulmonary function were encountered in this patient.

X-ray Manifestations

The typical appearance of primary pulmonary histiocytosis X on roentgenograms of the thorax is bilateral occurrence of diffuse symmetric, reticulonodular densities. These densities may vary in size, but average about 0.5 centimeter in diameter. Characteristically neither (all except cases 13 to 15, 19 and 25). Other investigators have noted the presence of erythema of the bronchial mucosa on bronchoscopic examination of patients with this disease.[10,14] This finding might account for the symptom of cough, or it might have been the result of coughing.

Despite the fact that widespread pulmonary involvement may be present in patients with primary pulmonary histiocytosis X, relatively few patients with this disease complain of dyspnea. The severity of this symptom, when it is present, appears to vary according to the extent and duration of the disease. Only three patients in the clinic series complained of dyspnea (cases 5, 6, and 7). It was a symptom in eight of the reported cases (cases 10, 12, 15, 21 to 23, 27 and 28). The patient with the most advanced dyspnea had been ill for at least 8 years and chronic cor pulmonale had developed.

It is recognized that spontaneous pneumothorax may occur rather frequently among patients with primary pulmonary histiocytosis X. This seems to be related to the known tendency of the disease to result in the formation of numerous small cysts. Three patients in the clinic

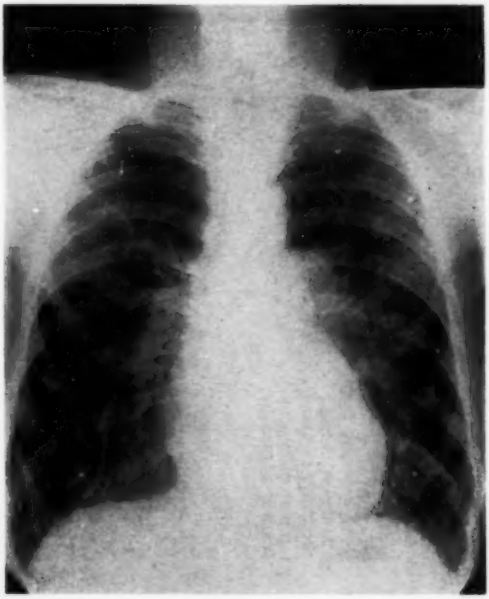

FIGURE 1: Primary pulmonary histiocytosis X of 9 years' duration (case 7). Typical roentgenogram of thorax with advanced honeycombing.

series had a history of spontaneous pneumothorax. One patient had recurrent pneumothoraces which led to the recommendation of parietal pleurectomy. During the performance of this procedure the diagnosis was established by biopsy of a specimen from the lung.

Finally, certain patients with primary pulmonary histiocytosis X may be completely asymptomatic. In such patients the disease may remain undetected until, for one reason or another, a roentgenogram of the thorax is made. In three cases reported in the literature primary pulmonary histiocytosis X was discovered in this manner.[12,14,17]

Physical Signs — Early in the course of the disease, physical examination of the patient with primary pulmonary histiocytosis X usually is not remarkable unless pneumothorax is present. Later on, as mentioned previously, there may be evidence of cor pulmonale and right heart failure. Lymphadenopathy, including enlargement of supraclavicular lymph nodes, splenomegaly and hepatomegaly are not encountered.

Laboratory Data

Unless chronic cor pulmonale is present, the red blood count and concentration of hemoglobin of patients with primary pulmonary histiocytosis X are usually within the normal range. The total and differential white blood counts are likewise normal as a rule, although occasionally mild eosinophilia (5 to 10 per cent) may bep resent.[9,12,14,16] The tuberculin skin test may show either positive or negative results. Cultures of the sputum or gastric washings for Mycobacterium tuberculosis and fungous organisms are uniformly negative.

Studies of pulmonary function were done on three clinic patients (table 3). Two of the three patients had rather extensive disease of relatively long duration. The tests showed abnormal results in these two patients, and data suggested the presence of both fibrotic and obstructive disease. In each instance the degree of abnormality of pulmonary function tended to correlate with the clinical status of the patient. Arterial oxygen desaturation developed on exertion in both patients. The third patient on whom pulmonary function studies were

TABLE 3 — RESULTS OF STUDY OF PULMONARY FUNCTION IN THREE PATIENTS WITH PRIMARY PULMONARY HISTIOCYTOSIS X (MAYO CLINIC SERIES)

		Degree of clinical disability and x-ray abnormality					
		Mild		Moderate		Severe	
		Estimated normal	Actual value (case 6)	Estimated normal	Actual value (case 4)	Estimated normal	Actual value (case 7)
Pulmonary volumes (liters)							
Vital capacity		4.6	3.7	3.2	1.8	4.5	1.7
Residual volume		1.5	1.5	1.2	1.4	1.5	2.7
Total capacity		6.1	5.2	4.4	3.2	6.0	4.4
Functional residual capacity		2.7	2.7	2.0	2.4	2.7	3.4
Maximal breathing capacity, liters per minute		141	116	83	49	120	39
Nitrogen-washout index (per cent)		<2.5	2.2	<2.5	1.0	<2.5	6.5
Oxygen saturation (per cent)	At rest	95 to 98	98	95 to 98	97	95 to 98	80
	After exercise	No decrease	98	No decrease	93	No decrease	79

enlargement of hilar or paratracheal lymph nodes nor pleural effusion is evident. Numerous small cystic areas may be evident throughout both lung fields. This produces a roentgenographic pattern that has been referred to as "honeycomb lung" (figure 1), a pattern which was observed in four of the seven clinic patients. Not infrequently, roentgenograms of the thorax also may show evidence of pneumothorax (figure 2). It has been noted previously that pneumothorax developed in three patients in the clinic series at one time or another during the course of their disease.

Few other diseases are capable of producing roentgenographic evidence of honeycomb lung. Sarcoidosis occasionally may cause "honeycombing," but when this occurs there is frequently an associated enlargement of the hilar and paratracheal lymph nodes. Honeycombing has likewise been observed in idiopathic pulmonary fibrosis (Hamman-Rich syndrome), in rare instances in which tuberous sclerosis involves the lungs, and in certain of the pneumonoconioses. However, the occurrence of pneumothorax in patients with these conditions is unusual. Therefore, the presence of pneumothorax together with evidence of honeycombing of the lungs on x-ray examination should cause strong suspicion of pulmonary histiocytosis, although such a finding is of course not diagnostic. X-ray findings consistent with histiocytosis were evident in five of the clinic cases and 18 of the cases in the literature. Data on these findings were not reported by one author.[13]

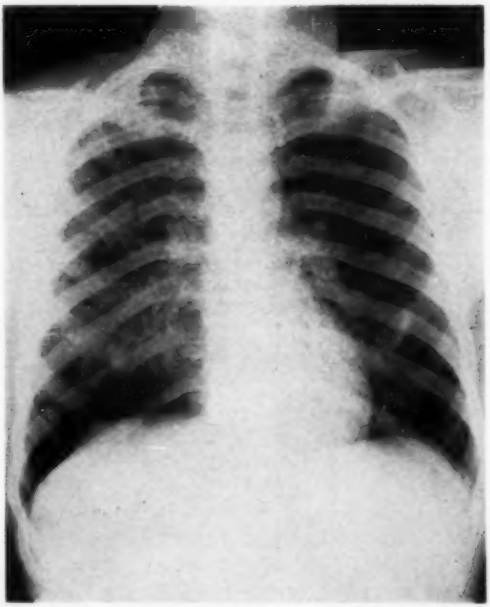

FIGURE 2: Primary pulmonary histiocytosis X or 2 years' duration (case 6). Typical roentgenogram of thorax with honeycombing and spontaneous pneumathoraces at the right base and left apex. A right parietal pleurectomy was done 1 year earlier, at the time of biopsy of lung tissue.

Occasionally roentgenograms of the thorax of a patient with primary pulmonary histiocytosis X will have an atypical appearance, which is suggestive of another disease entity. This was true in two patients in the clinic series (cases 2 and 3). In one patient the roentgenogram showed evidence of what appeared to be pneumonitis involving both lungs (figure 3). In the other patient there were bilateral nodular densities, larger than 1.5 cm. in diameter, which simulated metastatic carcinoma (figure 4). Unusual x-ray manifestations of pulmonary histiocytosis also have been observed by others. In one case reported in the literature there were x-ray findings suggestive of other disease (case 18). Arnett and Schulz,[14] noted bilateral enlargement of hilar lymph nodes which led to a tentative diagnosis of sarcoidosis.

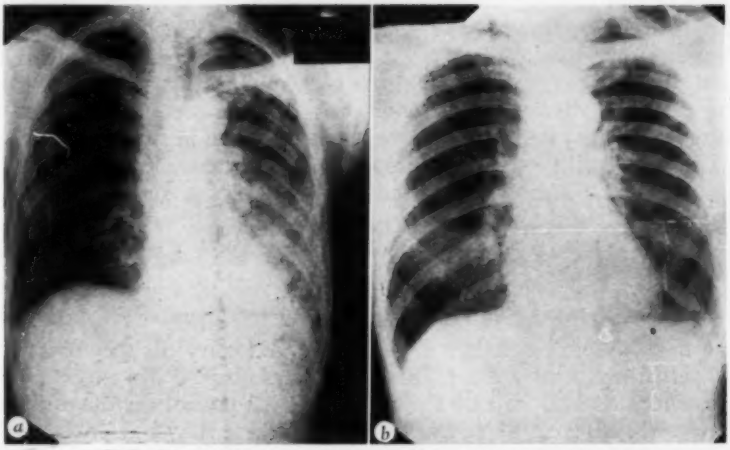

FIGURE 3: Primary pulmonary histiocytosis X presenting as bilateral pneumonitis (case 2). *a*. Roentgenogram 1 month after onset of symptoms. *b*. Roentgenogram after 3 months of treatment with prednisone. A specimen for biopsy was removed from the left lung.

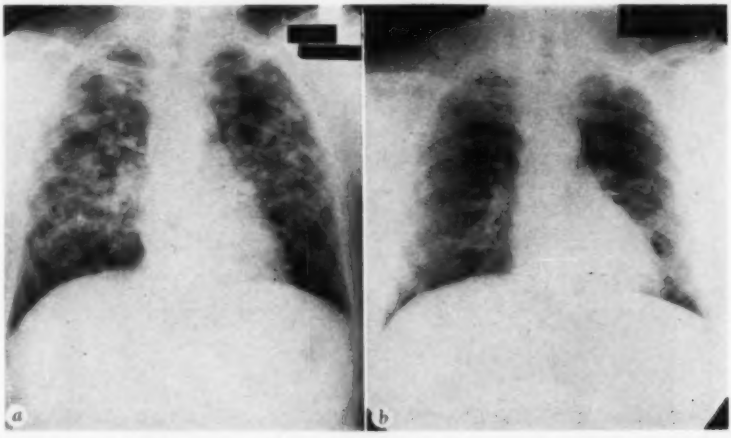

FIGURE 4: *a*. Roentgenogram showing atypical appearance of the thorax in case of primary pulmonary histiocytosis X (case 3). *b*. Same patient after 12 months of treatment with prednisone.

It is now well established that primary pulmonary histiocytosis X may be unilateral in its early stages. In one patient in the clinic series, the initial thoracic roentgenogram showed involvement of the right lower lung field only. A follow-up roentgenogram taken 2 months later showed what appeared to be typical bilateral disease. Arnett and Schulz[14] reported a similar sequence of events in one of their patients.

Diagnosis

The only way to establish a positive diagnosis of primary pulmonary histiocytosis X is by means of biopsy of a specimen from the lung. It is worth emphasizing that the specimen should be of generous size, at least 3 by 2 cm. broad and 3 to 4 mm. thick. Since the main pathologic feature of the disease is the presence of tiny isolated histiocytic infiltrates, a small specimen may show only normal lung tissue. Sections of frozen tissue prepared at the time of biopsy may be helpful in this regard. In one patient in the clinic series an initial section of frozen tissue failed to disclose any abnormality, and a second specimen was required for biopsy before a positive diagnosis could be made.

All patients with primary pulmonary histiocytosis X included in the clinic series and almost all patients whose cases were reported in the literature had undergone biopsy of prescalene lymph nodes prior to biopsy of lung tissue. In every instance biopsy of the lymph nodes gave negative results.

Pathologic Aspects

The microscopic pathology of primary pulmonary histiocytosis X has been well described by Auld,[16] and by Anderson and Foraker.[19] Despite the excellent descriptions by these authors, the pathologic diagnosis can be extremely difficult at times, since the disease may be confused with other conditions. We have reviewed the results of biopsy available in our seven patients. Additional sections were prepared from lung tissue

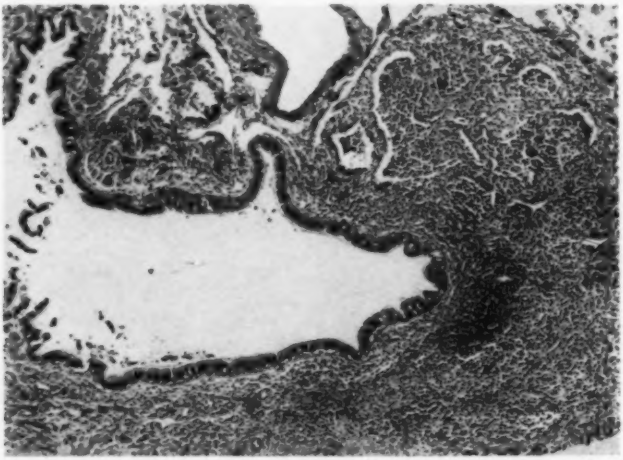

FIGURE 5: Characteristic histiocytic infiltration which contains eosinophils replacing parenchyma of lung and involving bronchiolar wall (case 1) (hematoxylin and eosin; x60).

and stained with hematoxylin and eosin, Lawson's modification of the elastic van Gieson stain and by Gomori's method for reticulin. The essential histologic feature required for a diagnosis of pulmonary histiocytosis X to be made is histiocytic infiltration of the alveolar septa and bronchiolar walls (figure 5). Eosinophils or giant cells also may be seen in regions infiltrated with histiocytes. Their presence lends further support to the diagnosis. However, the presence of eosinophils or giant cells is not an essential feature for the microscopic pathologic diagnosis of the disease.

It should be stressed that the mere finding of collections of histiocytes within the alveolar spaces does not entitle one to make a diagnosis of histiocytosis X. Intra-alveolar collections of histiocytes may be observed in a variety of unrelated diseases, including unresolved pneumonia. Two additional patients with clinical findings suggestive of primary pulmonary histiocytosis X have been excluded from the clinic series because biopsy of specimens of lung showed only intra-alveolar conglomerates of histiocytes.

At biopsy, specimens showing only cystic lung disease (figure 6) may support the clinical impression of primary pulmonary histiocytosis X, yet they are diagnostic only when the characteristic histiocytic infiltrations are found (figure 7). Thus "early" proliferative and destructive histiocytic foci in addition to so-called "late" fibrotic and cystic lesions may be present as a continuing disease process in the lungs.

Within these small focal infiltrations there is advanced parenchymal destruction which involves alveolar septa and bronchiolar walls (figure 7), as well as associated fragmentation and loss of elastic fibers of these structures, as pointed out by Anderson and Foraker.[19] Involvement of small arteries or arterioles by these infiltrates is frequently seen.[16,19] Thus, through necrosis of these infiltrates or their resorption or expulsion via bronchiolar communications, small parenchymal cavities may be formed

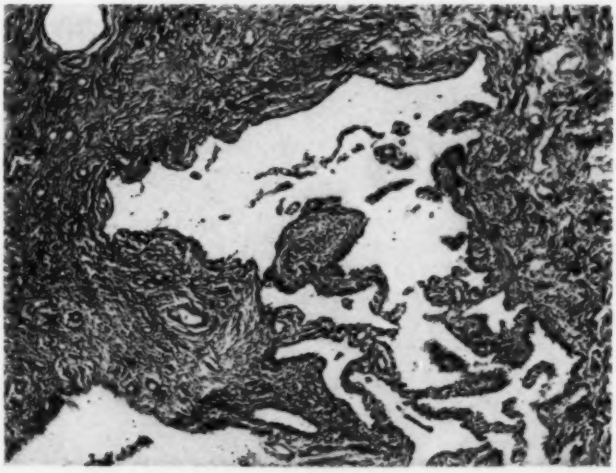

FIGURE 6: "Late" cystic formation in lungs (case 7). Cysts are lined by simple cuboidal or columnar epithelium or by fibrous tissue. Note fibrosis of parenchyma (left) (hematorylin and eosin; x65).

(figure 8). Repair of these lesions apparently is attempted because an abundance of reticulin fibrils is seen predominantly around the periphery of the histiocytic infiltrates. The reticulin is gradually replaced by proliferation of dense, fibrous tissue which usually makes up part of the walls of parenchymal cysts which have formed. Such a process eventually may lead to the formation of polycystic lungs in the advanced stage of this disease. Pneumothorax may result from rupture of one of these thin-walled cysts.

Auld[18] drew attention to the involvement of small pulmonary blood vessels which occurs in this disease (figure 8) and described a necrotiz-

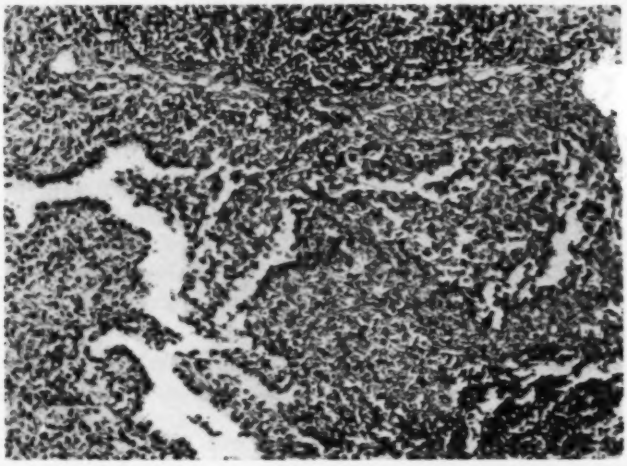

FIGURE 7: "Early" histiocytic infiltration with focal destruction of alveolar septa and bronchiolar wall (left) (case 7). From same biopsy specimen as figure 6 (hematoxylin and eosin; x140).

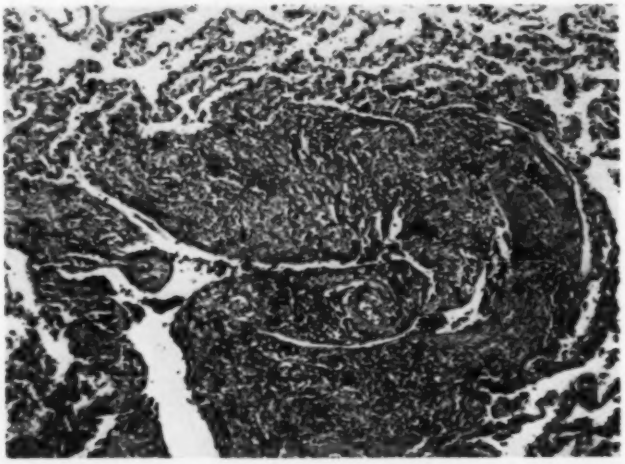

FIGURE 8: Slitlike cavity formation in central portion of histiocytic infiltrate communicating with a bronchiole (lower left) (case 6). Note involved arteriole in center of infiltrate (hematoxylin and eosin; x90).

ing arteriolitis in his cases. Our findings are similar to those of Anderson and Foraker[19] who demonstrated infiltration of histiocytes and eosinophils in the walls of small pulmonary blood vessels some of which also showed intimal proliferation and fragmentation of their elastica. In addition, some vessels were incorporated in zones of scarring. These vascular changes, the attenuation of the vessels in the walls of cysts, and the loss of part of the pulmonary vascular bed in regions of parenchymal destruction or scarring may lead to the eventual development of pulmonary hypertension and cor pulmonale when there has been extensive and long-standing involvement of the lungs.

Treatment

It is impossible at this time to assess adequately the value of any given form of treatment of primary pulmonary histiocytosis X for at least three reasons. 1. There appears to be a distinct tendency for the disease to undergo spontaneous exacerbations and remissions. This matter will be discussed further when the prognosis of the disease is considered. 2. Relatively few cases of this disease have been reported in the literature, and the patients have been observed for only limited periods after initiation of treatment. Proper evaluation of any therapeutic program under these circumstances is exceedingly difficult. Long-term follow-up studies of many more patients will be necessary before any positive statement can be made concerning the value of presently available therapeutic agents. 3. There is evidence to suggest that the results of any type of treatment are influenced, in part at least, by the stage of the disease at which treatment is begun. In general, the greater the extent and duration of the disease at the time treatment is started, the less likely it is that any given therapeutic agent will be effective.

X-ray therapy at times may cause regression of pulmonary lesions in patients with disseminated histiocytosis X in whom the lungs are involved secondarily. This observation led to a trial of x-ray therapy in one of our patients with primary pulmonary histiocytosis X (case 6). The results of treatment were disappointing. No immediate change in the x-ray appearance of the lungs was noted, and the patient returned 18 months after treatment with evidence of pneumothorax and progression of his disease. Other authors[14-16] have reported similar experiences with this form of treatment. Moreover, it is accepted that radiation therapy may cause pulmonary fibrosis, which is known to be one of the sequelae of the phase of active inflammation in pulmonary histiocytosis. One might justifiably be concerned about treating a disease capable of causing fibrosis with an agent that is likewise capable of causing fibrosis. At the present time x-ray therapy for primary pulmonary histiocytosis X seems to have been largely abandoned.

Following the lead of Lackey and associates,[20] a number of investigators have administered cortisone or one of its analogues to patients with this disease.[10,11,14-19] There would seem to be at least some rational basis for the use of these agents. Certain histiologic features of primary pulmonary histiocytosis X suggest the possibility that hypersensitivity may be an etiologic factor.[16] It has already been noted that tissue infiltration with eosinophils and peripheral eosinophilia may occur in patients with this disease. In addition, pulmonary vasculitis may be ob-

served occasionally on examination of microscopic sections of lung. Furthermore, it is recognized that cortisone and its analogues tend to prevent the formation of fibrous tissue and, as previously pointed out, fibrosis may occur after the active inflammatory phase of histiocytosis.

Five of the clinic patients were treated with cortisone or cortisonelike compounds (cases 1, 2, 3, 4, and 5). Admittedly, this is too small a number to permit any conclusion regarding the possible therapeutic value of these drugs. However, it is of interest that thoracic roentgenograms in three of the five cases showed evidence of definite regression of the lesions. All patients received treatment for several months. A fourth patient had been on treatment for only 6 weeks at the time of this report and definite change in the appearance of the roentgenogram had not been evident, although improvement was noted in certain pulmonary functions. The fifth patient had improved clinically, but we were unable to obtain a recent roentgenogram for comparison.

Among the 21 patients with primary pulmonary histiocytosis X whose cases are reported in the literature, 11 received treatment with cortisone or one of its analogues.[9-11,14-19] Three of the 11 patients had had symptoms of pulmonary insufficiency prior to treatment,[11,19] while eight had been almost asymptomatic. Following treatment, symptomatic improvement was noted in two of the three patients with pulmonary insufficiency.[19] The roentgenograms of most of the 11 patients who were treated with cortisone or related compounds showed evidence of improvement. However, roentgenograms of only two patients showed complete clearing of the lesions.[17,18] These two patients had had only minimal symptoms and their disease had been present for only a short time (6 to 12 months) before treatment was begun.

These observations suggest that treatment with cortisone or its analogues tends to produce beneficial results among patients with primary pulmonary histiocytosis X. It would appear that cortisone therapy is most likely to be effective when given early in the course of the disease. However, certain patients in whom the disease is far advanced and of long duration also may experience improvement after use of this drug. A therapeutic trial of cortisone or a cortisonelike compound would therefore seem warranted in all patients with proved primary pulmonary histiocytosis X. The problem of dosage schedules still remains to be settled.

Complications

There are three major complications of primary pulmonary histiocytosis X: spontaneous pneumothorax, diabetes insipidus, and chronic cor pulmonale.

As noted elsewhere, three clinic patients with this disease gave histories of spontaneous and, at times, recurring pneumothorax. In one of these patients simultaneous bilateral pneumothorax occurred. Heppleston[12] reported the case of a patient with primary pulmonary histiocytosis X whose death resulted from pneumothorax. Weiss and Johnston's[15] patient had recurring pneumothoraces and eventually required bilateral parietal pleurectomy. Certainly, the frequency with which pneumothorax occurs among patients with this disease and the poten-

tial seriousness of this complication are matters of grave concern to the patient and his physician. For this reason, when the clinical status of the patient permits, it might be well for the surgeon who obtains the specimen from the lung for biopsy to consider carrying out a procedure to promote pleural symphysis during the course of the operation.

Primary pulmonary histiocytosis X does not always remain confined to the lungs. Diabetes insipidus developed in three patients in the clinic series at varying intervals after the discovery of their pulmonary disease. In each instance diabetes insipidus presumably resulted from involvement of the hypothalamic-hypophyseal system by the disease process. Roentgenograms of the heads of these patients were without evidence of abnormality. A similar sequence of events was observed in the patient whose case was reported by Weiss and Johnston.[15] Other cases are reported in the literature in which primary pulmonary histiocytosis X and diabetes insipidus were both diagnosed at the same time.[11,21] It seems probable that in each of these cases the patient had pulmonary histiocytosis prior to the onset of diabetes insipidus, but the pulmonary disease was not discovered until the diabetes insipidus was studied.

Only one case has been reported in which pulmonary histiocytosis complicated by diabetes insipidus was studied at necropsy.[21] In this case the lungs and the hypothalamus were the only organs involved by the disease. Thus far, no case has been reported in which widespread, disseminated disease, either acute or chronic, has developed subsequently in a patient with primary pulmonary histiocytosis X. Insofar as can be determined, primary pulmonary histiocytosis X seems to invdlve either the lungs alone or, at most, the lungs initially and the hypothalamic-hypophyseal system secondarily.

Prognosis

Too few cases of primary pulmonary histiocytosis X have been reported up to the time of our study, and the follow-up periods have been too short to permit an accurate appraisal of the natural history of this disease. After reviewing the clinical histories of patients included in the clinic series and those whose cases are reported in the literature, the impression is gained that the disease, particularly when cortisone therapy is used, usually runs a rather mild course with a tendency toward remission. It is evident that in certain instances the disease may regress almost completely, even when no treatment is given. However, it is equally evident that despite intensive treatment the disease may at other times pursue a course of progressive deterioration toward severe pulmonary fibrosis and right heart failure. The variability and unpredictability of the clinical course of primary pulmonary histiocytosis X are well illustrated by the following case encountered at the clinic.

Report of Case

A 22-year-old man had apparently been in good health until a mildly productive cough developed. A roentgenogram of the thorax was taken and showed irregular areas of increased density in the upper two thirds of both lung fields. Because of this finding he was admitted to a tuberculosis sanatorium. Repeated cultures of sputum were made for Mycobacterium tuberculosis and fungi but all were negative. The patient's symptoms gradually subsided. The lesions seen on the first roentgenogram disappeared, and the patient was dismissed from the sanatorium 9 months after his admission. However, 2 years later, both the symptoms and the x-ray evidence

of pulmonary abnormalities reappeared and spontaneous pneumothorax developed. For the next 5 years the patient's cough persisted and he noted increasing shortness of breath. At the age of 29 years diabetes insipidus developed. He was first seen at the Mayo Clinic a year later, at which time there was evidence of fairly severe respiratory insufficiency and congestive cardiac failure. A specimen of lung tissue was obtained for biopsy and the diagnosis of histiocytosis X was established. The patient's condition became progressively worse and he died 6 weeks later.

Similar clinical histories have been reported by Heppleston[13] and by Spillane.[21]

Because the clinical course of primary pulmonary histiocytosis X is so unpredictable, the prognosis must at all times be guarded. Even if the disease undergoes complete remission, one cannot be certain that there will not be a recurrence which might possibly lead to death. Therefore, in the light of our present knowledge, it would seem wisest to treat actively all patients with primary pulmonary histiocytosis X until there is evidence of a remission of the disease. If complete remission does not occur, treatment should be continued until maximal improvement has been obtained and the clinical course of the patient has become stabilized. After remission or stabilization of the disease has occurred, follow-up physical and thoracic x-ray examinations should be made at regular intervals in order to detect any recurrence or exacerbation as early as possible.

SUMMARY

Data have been presented concerning seven patients with primary pulmonary histiocytosis X who have been seen at the Mayo Clinic, and 21 additional patients with this disease whose cases have been reported in the literature.

Primary pulmonary histiocytosis X is a disease of unknown etiology. It occurs more frequently in men than in women and is characterized from the pathologic standpoint by interstitial histiocytic infiltration and destruction of the parenchyma of the lung.

In general, the symptoms, physical signs, and laboratory data for these patients are rather nonspecific and of little diagnostic value. Nevertheless, roentgenograms of the thorax which show evidence of diffuse reticulonodular pulmonary fibrosis, particularly when associated with numerous small cystic areas (the "honeycomb lung"), should at least suggest the possibility of the disease. If, in addition to these x-ray findings, there is evidence of one of the known complications of the disease, such as spontaneous pneumothorax or diabetes insipidus, the possibility of primary pulmonary histiocytosis X should be strongly considered. However, a positive diagnosis can be established only by biopsy of a specimen from the lungs.

The clinical course of primary pulmonary histiocytosis X is both variable and unpredictable. For this reason the prognosis should always be guarded. As a rule, the disease runs a mild and chronic course with a tendency toward remission. However, at times it may progress relentlessly to the point of severe pulmonary fibrosis, cor pulmonale, and congestive cardiac failure.

At the time of this study, cortisone or cortisonelike preparations given early in the course of the disease would seem to be the treatment of choice for primary pulmonary histiocytosis X.

Too few cases of primary pulmonary histiocytosis X have been reported and follow-up study in the cases that have already been reported has not been long enough to provide much knowledge about the natural history of the disease and the value of various forms of treatment, including that with cortisone.

RESUMEN

Se han presentado los datos de siete enfermos con histiocitosis pulmonar primaria que se han visto en la Clínica Mayo y 21 enfermo mas con esta enfermedad que se han relatado en la literatura.

La histiocitosis primaria pulmonar es una enfermedad de etiología desconocida. Se presenta mas frecuentemente en hombres que en las mujeres y se caracteriza desde el punto de vista quotomopatológico por una infiltración intersticial histiocítica y destrucción del parenquima pulmonar.

En general los síntomas, los signos físicos, y los hallazgos de laboratorio de estos enfermos, son mas bien inespecíficos y de escaso valor diagnóstico. Sin embargo las radiografías del tórax que muestran evidencias de fibrosis reticulonodular, particularmente cuando se asocian a numerosas áreas císticas (pulmón en panal) deben por lo menos sugerir la enfermedad.

Si ademas de estos hallazgos radiológicos hay evidencia de una de las conocidas complicaciones tales como neumotórax espontáneo, o diabetes insípida, la posibilidad de que se trate de histiocitosis pulmonar debe ser considerada como sólida. Sin embargo un diagnóstico positivo se puede establecer sólo por un especimen de biopsia pulmonar.

La evolución de la histiocitosis pulmonar primaria es variable e impredecible. Por esto el pronóstico debe ser siempre reservado.

Como regla la enfermedad tiene una evolución moderada y crónica con tendencia a la remisión. No obstante, a veces puede evolucionar sin remisión hasta llegar a la fibrosis pulmonar grave, cor pulmonale e insuficiencia cardiaca congestiva.

Hasta el momento de este estudio, la cortisona y análogos proporcionados tempranamente, parecen el tratamiento de elección para esta enfermedad.

Se han relatado demasiado pocos casos de histiocitosis primaria pulmonar y su sequimiento a través del tiempo, no ha sido suficientemente largo para proporcionar conocimiento de su historia natural y sobre el valor de los diversos tratamientos incluyendo el de la cortisona.

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Pulmonary Infiltration Associated with Blood Eosinophilia (P.I.E.): A Clinical Study of Loeffler's Syndrome and of Periarteritis Nodosa with P.I.E. Syndrome*

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Infiltration of the pulmonary parenchyma may be seen in the thoracic roentgenogram in a variety of diseases. Such infiltration may be associated with eosinophilia of the peripheral blood, and when this association occurs, the descriptive term "pulmonary infiltration with eosinophilia" (P.I.E. syndrome) is used. It is seen in Loeffler's syndrome, sometimes in periarteritis nodosa, in certain bacterial and mycotic infections, in some parasitic infestations and in tropical eosinophilia or Weingarten's syndrome. Rarely, it may be a feature of Wegener's granulomatosis or of eosinophilic granuloma of the lung, or it may occur with drug reactions. In a nontropical area when no infecting or infesting agent can be demonstrated, the usual problem is to distinguish between the essentially benign Loeffler's syndrome and the pulmonary infiltration occasionally associated with periarteritis nodosa and blood eosinophilia. The present study was undertaken to compare the features of these two conditions.

Clinical Material and Methods

A review was made of the records of 30 patients in whom the clinical diagnosis of Loeffler's syndrome was felt to be established, and of 13 patients with periarteritis nodosa who presented the P.I.E. syndrome; these 13 patients were among 125 with microscopically proved periarteritis nodosa. Diagnosis of the latter was confirmed by microscopic examination of the tissues in each instance, either following muscle biopsy or at necropsy. All the patients included in this study had pulmonary parenchymal infiltrates associated with peripheral blood eosinophilia in excess of 5 per cent of the total leukocyte count. All studies of stools for parasites and of sputum for malignant cells gave negative results. Cultures of sputum and gastric or bronchial washings failed to disclose tubercle bacilli, fungi or pathogenic bacteria in any instance. The asthmatic and allergic history of each patient, the behavior of the pulmonary infiltrates and their association with attacks of asthma, the pertinent laboratory data, and the significant clinical manifestations were studied and the results in the one group compared with those in the other. The following illustrative cases demonstrate the salient features of the two conditions.

Illustrative Cases

Case 1: (Loeffler's syndrome.) A 33-year old white married woman gave a strong family history of asthma. She herself had had bronchial asthma for 17 years and

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hay fever for 10 of these, particularly in August and September. The latter was relieved to some extent by desensitization. For about 1 month before admission, she had run a fever (temperature of 100° F.), had had almost constant wheezing, shortness of breath and a cough, and had produced 4 teaspoonfuls of mucoid, yellowish sputum daily. Antiasthmatic therapy at home had not relieved her attack on this occasion and she was admitted to the hospital where antibiotics were added to her antiasthmatic program. The results of physical examination were not remarkable apart from considerable diffuse bronchospasm throughout both lungs. The important laboratory data were a leukocyte count of 16,400 cells per cubic millimeter of blood, with 43 per cent eosinophils, and an erythrocytic sedimentation rate of 58 mm. in 1 hour. Two stool examinations were negative for parasites and ova. Skin tests for tuberculosis, histoplasmosis and coccidioidomycosis all gave negative results. Sputum examination for acid-fast bacilli in a stained specimen also gave negative results. X-ray examination of the thorax showed changes in the right upper lobe which suggested the possibility of active pulmonary tuberculosis. Because of her negative tuberculin reaction, the absence of acid-fast bacilli in a stained smear of sputum, and her clinical state, tuberculosis was thought unlikely and treatment with ACTH was started after the x-ray opacities had spread throughout both lungs (figure 1*a*). Following institution of this therapy, the lungs cleared remarkably and her pulmonary symptoms disappeared completely, with marked relief of her asthma (figure 1*b*). The clinical diagnosis was Loeffler's syndrome.

Case 2: (Pulmonary infiltration associated with periarteritis nodosa and blood eosinophilia). The patient was a 65-year-old white man with no previous personal or family history of allergy or bronchial asthma. Three months before admission, he developed cough and low-grade fever and produced a half cupful of yellow-green mucoid sputum daily. Within the following month, his activity became considerably restricted by increasing dyspnea and wheezing. Because of these symptoms he was hospitalized elsewhere, where a roentgenogram revealed an area of pneumonitis in the left upper lobe which was diagnosed as Friedlander's pneumonia; this was treated with appropriate antibiotics. Then the patient's condition improved, and for the next 4 weeks he remained relatively free of symptoms. Subsequently, he began to notice loss of weight and the development of a purpuric eruption on both lower limbs. At this time also he had transient diplopia with total but temporary blindness of the right eye. He was found to be anemic and began to suffer pain in the right calf with attendant numbness in the foot, which caused considerable difficulty in walking. Shortly before admission, he began to have hemoptysis.

On physical examination, he was found to have a low-grade fever and appeared chronically ill. Apart from a few scattered crepitant rales throughout both lungs, there was nothing of significance on auscultation. Temperature and blood pressure were within normal limits. A purpuric eruption was present over the lower extremities, the right ankle jerk was absent and there was dropped right foot. Examination of the ocular fundi did not reveal any gross abnormality. The neurologic deficit was thought to be consistent with a diagnosis of mononeuritis multiplex. The value for hemoglobin was 8.7 gm. per 100 ml. of blood, and the leukocyte count was 14,100, with 23 per cent of the cells being eosinophils. The erythrocytic sedimentation rate was 88 mm. in 1 hour. Blood urea measured 198 mg. per 100 ml. Urinalysis revealed an acid urine with a specific gravity of 1.008, and grade 1 albuminuria and grade 3 micro-

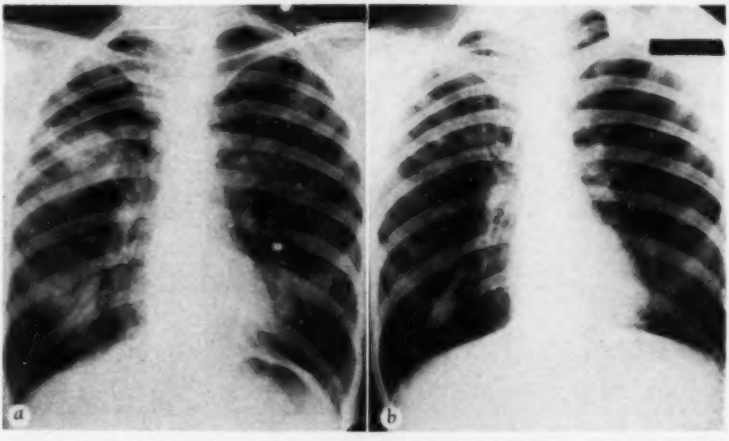

FIGURE 1 (case 1) *a* and *b*: Remarkable clearing of the lungs has occurred in the interval of 12 days represented by the roentgenograms. This followed administration of ACTH and was accompanied by complete relief of symptoms.

TABLE 1—VITAL STATISTICS AND ASTHMATIC AND ALLERGIC HISTORY IN 30 CASES OF LOEFFLER'S SYNDROME AND 13 CASES OF PERIARTERITIS NODOSA ASSOCIATED WITH P.I.E. SYNDROME

	Loeffler's syndrome	Periarteritis nodosa with P.I.E. syndrome
Average age, years	38	53
Ratio of males to females	14:16	7.6
Family or personal history of allergy, cases	23	7
History of bronchial asthma, cases	23	1
Average duration of bronchial asthma, years	8	20

hematuria. Clinically, a diagnosis of periarteritis nodosa was made, but biopsy of the left gastrocnemius muscle did not show the changes of this disease. X-ray examination showed pneumonitis in the upper lobe of the right lung (figure 2*a*.).

Treatment was begun with supportive blood transfusions and with cortisone. Despite this, the patient's condition continued to go downhill, with increasing toxicity, weakness and hemoptysis. On the fourteenth hospital day, hemoptysis became profuse, and coarse, moist sounds could be heard throughout both lungs. Tachycardia and dyspnea increased considerably. Over the next few days hemoptysis continued, and further x-ray examination showed bilateral patchy infiltrates in both lungs, interpreted initially as due to congestive heart failure (figure 2*b*.). His condition improved clinically but the blood urea increased steadily, and it was suspected that the x-ray changes in his lungs did not represent pulmonary edema but necrotizing alveolitis. On the twentieth hospital day he had a convulsion, passed into coma and rapidly died. At necropsy, typical lesions of periarteritis nodosa were identified in the kidneys, abdominal viscera, muscles and brain. The immediate cause of death was an infarct in the right occipital lobe. Changes compatible with necrotizing alveolitis were present in both lungs.[1]

Analysis of Cases

The incidence of combined pulmonary infiltration and blood eosinophilia associated with periarteritis nodosa was found not to be high. Thus, of the 125 patients with a microscopically proved diagnosis of periarteritis nodosa, blood eosinophilia was found in 37 (30 per cent). However, the combination of pulmonary infiltration with eosinophilia occurred in only 13, an incidence of about 10 per cent. For the entire series of 43 patients studied, the sexes were about equally represented, and a strong background of allergy was mentioned in either the personal

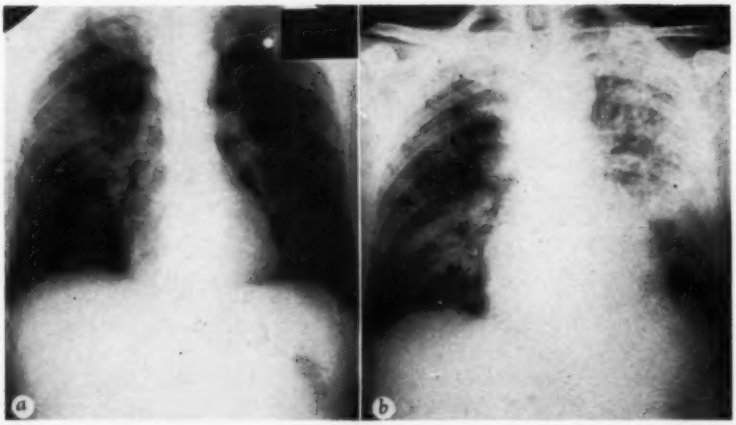

FIGURE 2 (case 2) *a* and *b*: The roentgenograms were taken 14 days apart. The pathologic process has progressed during this time despite the ues of ACTH. The second roentgenogram was taken 4 days before death. At necropsy, changes compatible with necrotizing alveolitis were present in both lungs.

TABLE 2—PULMONARY INFILTRATION ASSOCIATED WITH PERIPHERAL BLOOD EOSINOPHILIA, CONCURRENT ASTHMATIC ATTACKS, AND ROENTGENOLOGIC FINDINGS

	Loeffler's syndrome, cases	Periarteritis nodosa with P.I.E. syndrome, cases
Pulmonary infiltration with eosinophilia	30	13
Attacks		
One	19	13
More than one	11	—
Asthma with P.I.E.	26	7
Duration		
Two months or less	21	—
More than 2 months	5	7
Roentgenologic findings		
Unilateral infiltrates	9	3
Bilateral infiltrates	21	10

or the family history. The patients with Loeffler's syndrome were, on the average, 15 years younger than those with periarteritis nodosa and the P.I.E. syndrome. Only one patient with periarteritis nodosa had had a previous history of bronchial asthma, whereas 23 patients in the other group had had this condition for an average duration of 8 years (table 1).

Many patients with Loeffler's syndrome had recurrent attacks of pulmonary infiltration with eosinophilia, and the asthma associated with these attacks was of shorter duration than that associated with periarteritis nodosa. Most patients with Loeffler's syndrome had had attacks of asthma of less than 2 months' duration. The roentgenologic findings were not pathognomonic, and while the majority had bilateral infiltrates, patients in whom the infiltrates remained unilateral were seen in both groups (table 2). The most consistently helpful laboratory aids in differentiating the two groups were the values for hemoglobin and blood urea. Almost all the patients with periarteritis nodosa tended to have a degree of anemia varying from mild to moderate. Eight of them had evidence of advanced renal disease, and the value for blood urea in these individuals averaged 126 mg. There was no evidence of renal disease complicating Loeffler's syndrome. Although the sedimentation rate appeared to be higher, on the average, in periarteritis nodosa, this was not considered of real diagnostic value although it was felt to increase the suspicion of that disease (table 3).

The incidence of hemoptysis was much higher in periarteritis nodosa than in Loeffler's syndrome, and six of the 13 patients had such a history compared with only four in the other group, of whom two also had

TABLE 3—AVERAGE VALUES FOR SIGNIFICANT LABORATORY DATA

	Loeffler's syndrome	Periarteritis nodosa with P.I.E. syndrome
Hemoglobin, gm. per 100 ml.	13.3	11.2
Leukocytes per cubic millimeter	11,800	15,300
Eosinophils, per cent of total leukocytes	26	38
Erythrocytic sedimentation rate in excess of 20 mm. in 1 hour	55 (14 patients)	80
Blood urea in excess of 40 mg. per 100 ml.	—	126 (8 patients)

bronchiectasis. The incidence of pleural effusion was also higher in periarteritis nodosa, and in two of the three patients in whom it occurred the effusions were bilateral. The skin lesions of periarteritis nodosa tended to be purpuric or ecchymotic, but in the other group they were nonspecific in most instances and in some were thought to be responsible for the eosinophilia.

Evidence of disease of multiple systems in the patients who suffered from periarteritis nodosa was most important. Of five deaths occurring during the attack of P.I.E. syndrome, all resulted from renal failure. The neurologic involvement produced a peripheral neuropathy principally of the mononeuritis multiplex type. Joint symptoms followed the pattern of a rheumatoid type of arthritis. Cardiac involvement, in two cases, produced pericarditis in one and gallop rhythm in the other. Necrotizing alveolitis was present in two patients and was preterminal in both instances (table 4).

Fourteen patients with Loeffler's syndrome treated with steroids obtained prompt relief of symptoms, with dramatic clearing of the thoracic roentgenogram and return of the eosinophil count to within normal limits in every instance. Other forms of treatment were less effective. Steroids were given to all 13 patients with periarteritis nodosa. Despite this, six died, although the disease was controlled satisfactorily in the remaining seven patients for periods ranging up to 3 years from the start of treatment. Systemic disease did not develop in any patient with Loeffler's syndrome during observation periods lasting from 4 months to 10 years from the first attack.

Observations by Others

In 1932, Loeffler first described the syndrome that has come to bear his name.[2] He stressed the transient nature of the pulmonary infiltrates and the absence of parasitic infestation in the patients he studied. He also pointed out that the picture was not pathognomonic of any one etiologic factor, but wondered whether the infiltrates did not represent changes of early tuberculosis. Four years later, he offered the concept that an allergic mechanism might be responsible, and there has been general agreement since then that the pneumonic consolidations seen in this syndrome are allergic in nature.[3] Loeffler also observed that al-

TABLE 4 — SIGNIFICANT CLINICAL MANIFESTATIONS

	Loeffler's syndrome, cases	Periarteritis nodosa with P.I.E. syndrome, cases
Hemoptysis	4*	6
Pleural effusion	1	3
Skin lesions	6†	8
Renal disease	—	8
Neurologic involvement	—	8
Joint symptoms	—	7
Cardiac involvement	—	2
Necrotizing alveolitis	—	2
Death during attack of P.I.E.	—	5

*Two with bronchiectasis.
†Ioderma, dermographia and miscellaneous eruptions.

though the eosinophil count might go as high as 60 per cent, the degree of eosinophilia did not parallel the extent of the pulmonary shadows, which might clear in a few days or persist for weeks or months in the absence of treatment.

Although Loeffler's syndrome is observed most frequently in asthmatic patients, this does not imply that asthma is an essential feature of the syndrome, which may be associated with other allergic manifestations int he absence of asthma.[4] When bronchial asthma is a feature, it may be persistent and severe while pulmonary consolidations are present. Conversely, the variable and polymorphic shadows are frequently extensive and out of proportion to the mildness of the symptoms. Ham and Zimdahl[5] have stressed that cases fitting into the symptom complex as first described should be called cases of Loeffler's syndrome, but that all other cases should be termed cases of pulmonary infiltration with blood eosinophilia of known or unknown cause. Individual cases have been described as associated with hypogammaglobulinemia[6] and with increased urinary excretion of histamine.[7] Various drugs, including antituberculous drugs, have been associated with the syndrome.[8,9]

Gravesen[10] has suggested that it is the interstitial tissue of the lung that is hypersensitive, rather than that of the bronchi as in bronchial asthma. Harkavy[11] has proposed that recurrent and transient pulmonary infiltrates with eosinophilia may represent one manifestation or phase of vascular allergy, and Engel[12] has regarded the pulmonary changes as a form of Quincke's edema and has proposed the term "edema allergicum pulmonis."

The outstanding histologic features of the pulmonary lesions in Loeffler's syndrome as described by Bayley and associates[13] were the large numbers of eosinophilic leukocytes in the pneumonic exudate, the advanced organization of the exudate, the fibrosis and giant cells, the presence of peculiar granulomatous lesions, and the occurrence of necrotizing arteritis and phlebitis. These vascular lesions were striking and were similar histologically to the changes seen in periarteritis nodosa. Von Meyenburg[14] also observed infiltrates of pneumonic type, and alveolar exudates with eosinophilic infiltration into the alveoli and interstitial tissue of the lung.

The cardinal clinical features of Loeffler's syndrome are the absence of a specific infecting agent or infesting parasite, and its benign course. These features were well illustrated in the 30 patients described in the present series; all but four had bronchial asthma in association with their pulmonary infiltrates and blood eosinophilia. The other four suffered from skin eruptions which were thought responsible for the eosinophilia. All the patients recover completely and the course was essentially benign, with dramatic response of the clinical and roentgenologic abnormalities to treatment with steroids when these were used. There was no evidence of systemic disease or infecting or infesting agents.

Periarteritis nodosa is a disseminated disease of unknown origin, characterized by focal inflammatory lesions that involve chiefly the smaller arteries and arterioles of many organs and tissues. While there appear to be multiple etiologic factors, allergy is thought to play a part in the development of this disease. It may occasionally be associated

with pulmonary infiltration and eosinophilia, and its variable to poor prognosis causes it to assume importance in the differential diagnosis of the P.I.E. syndrome. The pulmonary manifestations of periarteritis nodosa are also variable and the response of this disease to steroids is unpredictable.[15] Infiltrates, consolidations, abscesses or cavities may be seen on the thoracic roentgenogram. Usually, a constitutional illness is obvious and a family history of asthma is often absent. Rose[16] felt that there was no difference microscopically between the lesions in individuals with pulmonary involvement and in those without it. He felt that pulmonary lesions preceded the systemic illness by several years. However, Doub and associates[17] considered that major pulmonary symptoms or parenchymal x-ray abnormalities indicated a poor prognosis in patients with periarteritis nodosa and were a manifestation of widespread systemic disease. They did not believe that x-ray abnormalities were specific, although at times they could be suggestive. At necropsy, they observed changes in both the pulmonary and the bronchial arteries together or individually.

The reported incidence of pulmonary involvement in periarteritis nodosa has varied from 18 per cent to 29 per cent in different series,[18-20] but the incidence of such involvement with attendant blood eosinophilia is not so well documented. In the present series, all patients with pulmonary involvement were found to have a poor prognosis, and the pulmonary changes were regarded as an indication of severe systemic involvement. Sweeney and Baggenstoss[21] have described the pathologic changes in the pulmonary lesions of periarteritis nodosa, and have noted that perivascular pneumonia with granulomas and scars are the main changes observed. Acute granulomatous and healed lesions of the vessels and parenchyma were found, together with perivascular pneumonia and alveolar exudates. Granulomas and giant cells were predominant, and it was considered that the granulomas were of allergic origin. The changes of necrotizing alveolitis have also been regarded as due to hypersensitivity.[21]

From the present study, it would seem that the more protracted the attack of pulmonary infiltration and peripheral blood eosinophilia, especially if it is the first known attack, the more likely is the disease to be periarteritis nodosa. Hemoptysis is relatively common, and evidence of multiple-system involvement is conclusive. This may be demonstrated by the presence of purpuric lesions, mononeuritis multiplex, arthritic symptoms and, most significantly, uremia. The grave illness and steady downhill course militat[illegible] against Loeffler's syndrome and are more compatible with a diagnosis [illegible] periarteritis nodosa.

Pulmonary infiltration with blood eosinophilia may also be produced by bacterial infections, but this combination is relatively rare. As more attention is paid to laboratory culture of the organism for final proof of the nature of the infection, these associations with bacterial infections become less impressive. However, it appears to be well substantiated that mycotic infections are responsible for the syndrome in a few cases[22]. The chief offenders are coccidioidomycosis, histoplasmosis and aspergillosis. While skin and serologic tests may be useful in raising

the suspicion of a fungous infection, final proof rests on culture of the offending organism from available pathologic material.

Certain nematodes, cestodes, trematodes and amebas have been reported to produce the P.I.E. syndrome.[23] The pneumonic areas are usually transient and, in the case of worms or flukes, are thought to be associated with passage of one phase of the life cycle of the parasite through the lungs. The diagnosis is made by finding one form of the parasite in stool specimens or, less commonly, in sputum.

Tropical eosinophilia was described in 1943 by Weingarten.[24] It is endemic in some tropical and semitropical regions of Asia and South America and is associated with extensive pulmonary infiltrates and peripheral blood eosinophilia. Cough, dyspnea and asthmatic paroxysms may be severe and persist for months at a time, with frequent and ready relapse over several years. There is no allergic background in these patients, and no deaths have been reported. The response to treatment with arsenicals is prompt and specific. The exact location of this disease in the spectrum of diseases associated with the P.I.E. syndrome is not yet determined, and further investigation is necessary to clarify the exact nature of this condition. Some patients thought to be suffering from this disease have been found to harbor parasites, but apparently expulsion of the parasite does not relieve tropical eosinophilia clinically.

A combination of atypical x-ray findings, with allergic symptoms, eosinophilia, facial or skin granulomas, or severe renal disease, is found in the noninfectious necrotizing granulomatoses. These include Wegener's syndrome, lethal granuloma of the midline, and allergic angiitis and granulomatosis.[25] Eosinophilia is present in Wegener's granulomatosis in almost half the patients, and is occasionally seen in combination with pulmonary changes on the thoracic roentgenogram.[26] This condition is characterized by granulomatous lesions with necrosis in the upper air passages and also at times in the lower respiratory tract, a widespread vasculitis, and a granulomatous necrotizing glomerulitis. It is usually fatal in 7 to 12 months. Lethal midline granuloma also is a serious disease and may be closely related to Wegener's granulomatosis or be a local form of it. It does not have the pulmonary and vascular component of the more widespread disease. Chung and Strauss[27] described allergic angiitis and granulomatosis as characterized by asthma, fever, eosinophilia, necrotizing angiitis, extravascular granulomas, cutaneous lesions and recurrent pneumonias. Like Wegener's granulomatosis, its relationship to periarteritis nodosa is uncertain.

Less than 5 per cent of cases of eosinophilia granuloma of the lung are associated with peripheral blood eosinophilia, but in this small number the presenting features may be those of the P.I.E. syndrome.[28] It has been suggested that Loeffler's syndrome may be an early stage of eosinophilic granuloma of the lung, or of periarteritis nodosa,[29] but there is no support from the present study for this concept.

A combination of pulmonary infiltration with eosinophilia might occur in some cases of Hodgkin's disease or carcinomatosis, coincidentally with familial eosinophilia, after irradiation or splenectomy, or in other conditions attended by eosinophilia.[30] The importance of these combinations is more theoretic than real, and for practical purposes they can be discounted.

SUMMARY

The problem of pulmonary infiltrations with blood eosinophilia has been reviewed. A clinical study was made of 30 patients in whom a diagnosis of Loeffler's syndrome was thought to be established on clinical grounds, and of 13 patients in whom a diagnosis of periarteritis nodosa with the syndrome of pulmonary infiltration associated with eosinophilia (P.I.E.) was established by microscopic means. A history of bronchial asthma extending over several years and the occurrence of more than one attack of pulmonary infiltration and eosinophilia are more in keeping with Loeffler's syndrome. The longer the attack of the P.I.E. syndrome, especially if it is the first known attack, the more likely is the disease to be periarteritis nodosa. Hemoptysis is more common with the latter, and evidence of multiple-system involvement is conclusive. This may be shown by purpuric lesions, mononeuritis multiplex, arthritic symptoms and uremia. If the patient appears gravely ill and is pursuing a steadily downhill course, then Loeffler's syndrome is almost surely excluded.

RESUMEN

Se ha revisado el problema de las infiltraciones pulmonares en las que hay eosineofilia sanguínea. Se hizo un estudio clínico en 30 enfermos en los que se hizo el diagnóstico de síndrome de Loeffler basándose en los hallazgos clínicos, y de 13 enfermos en los que se hizo el diagnóstico de periarteritis nodosa, con el síndrome de infiltración pulmonar asociada coneosinofilia. (P.I.E.) de acuerdo con los hallazgos al microscopio.

Cuando hay antecedentes de asma bronquial de dos años de duración y uno o mas ataques de infiltración pulmonar con eosinofilia, es mas de inclinarse hacia al diagnóstico de síndrome de Loeffler.

Caundo los ataques del síndrome de infiltración pulmonar eosinófila, especialmente sí se trata del primer ataque conocido, es mas posible que se trate de periarteritis nodosa. La hemoptisis es mas común en la última y la evidencia de compromiso de sistemas múltiples es concluyente. Esto puede mostrarse por lesiones púricas, mononeuritis, o múltiple, síntomas artríticos y uremia.

Si el enfermo parece gravemente afectado y sigue una evolución con deterioro progresivo entonces casi seguramente stá excluído el síndrome de Loeffler.

RESUMÉ

Les auteurs étudient la question des infiltrats pulmonaires avec éosinophilie sanguine. Une étude clinique a été faite pour 30 malades chez lesquels le diagnostic de syndrome de Loeffler était établi sur des bases cliniques, et pour 13 malades chez lesquels le diagnostic de péri-artérite noueuse avec syndrome d'infiltrat pulmonaire associé à une éosinophilie fut fondé sur les examens microscopiques.

Une histoire d'asthme bronchique s'étendant sur plusieurs années, et l'apparition de plusieurs poussées successives d'infiltrats pulmonaires avec éosinophilie sont plus en faveur d'un syndrome de Loeffler. Plus l'infiltrat avec éosinophilie est lent à se résoreber, surtout s'il s'agit de la première manifestation, plus est vraisemblable le diagnostic de périartérite noueuse. L'hémoptysie est plus commune dans ce dernier cas et la mise en évidence d'autres atteintes viscérales est concluante. Elles peuvent se manifester par des lésions purpuriques, des manifestations polynévritiques, des symptômes articulaires et de l'urémie. Si le malade semble gravement atteint et semble faire une évolution lentement fatale, le syndrome de Loeffler est alors presque sûremen éliminé.

ZUSAMMENFASSUNG

Übersicht des Problems der Lungeninfiltrate in Zusammenhang mit einer Eosinophilie des Blutes. Es wurde eine klinische Analyse vorgenommen von 30 Patienten, bei denen aus klinischen Gründen die Diagnose eines Löffflerschen Syndrome als gesichert worden war, und von 13 Patienten, bei denen die Diagnose einer Periarteritis nodosa mit dem Syndrom pulmonaler Infiltration in Verbindung mit Eosinophilie (P.I.E.) mikroskopisch gesichert war. Eine Vorgeschichte mit Bronchial-Asthma, das sich über mehrere Jahre erstreckte, und das Auftreten von mehr als einer Attacke pulmonaler Infiltration und Eosinophilie stehen mehr im Einklang mit dem Löffflier'schen Syndrom. Je länger die Attacke des P.I.E. — Syndroms anhält, zumal wenn es der erste bekannte Anfall ist, mit desto grösserer Wahrscheinlichkeit handelt es sich bei der Erkrankung um eine periarteritis nodosa. Bei letzterer kommt eine Haemoptyse häufiger vor, und der Nachweis des Betroffenseinsmultipler Organsysteme ist entscheidend. Dies lässt sich nachweisen an purpura-ähnlichen Herden, einer Mononeuritis multiplex, an arthritischen Symptomen und Urämie. Erscheint der Patient schwer krank, und nimmt das Geschhen einen unaufhaltsam ungünstigen Verlauf, so ist das Löffflier'sche Syndrom fast mit Sicherheit auszuschliessen.

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Papilledema in Patients with Severe Pulmonary Emphysema*

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Abnormalities of function of the central nervous system that occur in association with severe pulmonary emphysema have been reported with increasing frequency. This trend may represent an increase in the actual incidence of severe emphysema but it also may reflect a better understanding of mechanisms involved and consequently a greater index of awareness by clinical observers. The paradoxical manifestations of both depression and irritability of the central nervous system have been attributed to hypoxia, hypercapnia, polycythemia, cor pulmonale and alterations in cerebral blood flow with associated increase in cerebrospinal fluid pressure.

A small portion of these patients manifesting one or more of the features of headache, mental cloudiness and muscular twitching in addition to signs of pulmonary insufficiency may be found to have varying degrees of papilledema.[1-11] Sieker and Hickam[7] reported that one patient in their series of 25 patients with classic carbon dioxide intoxication complicating severe chronic pulmonary insufficiency had papilledema. Numerous others have described the finding of papilledema in such patients which usually led to detailed investigation of the central nervous system to eliminate the possibility of an expanding intracranial lesion. The patient's altered sensorium often thwarted the physician's efforts to elicit the cause of the papilledema and necessitated the accumulation of objective evidence to exclude the presence of a brain tumor.

The purpose of this paper is to add to the small but growing number of cases which have been reported and to gain additional information about the clinical ramifications of this problem.

Report of Cases

Case 1: A 52-year-old machinist registered at the Mayo Clinic on August 9, 1957, complaining of shortness of breath for 2 years, first noted when he tried pushing his car in cold weather. For many years prior to this he had had cough in the morning with expectoration of 1 ounce of yellow to gray sputum. He had smoked one package of cigarettes daily for many years. Waves of nausea had troubled him at times during meals but there had been no vomiting and no heartburn. To aid in breathing he had taken pills which also made him sleepy. For about 2 weeks prior to his registration he had been taking cortisone. Dyspnea had progressed so that he was out of breath after walking one block at a normal pace. He denied having thoracic pain.

On physical examination he weighed 137 pounds and his height was 5 feet, 3¼ inches. His blood pressure measured 170 mm. of mercury systolic and 105 mm. diastolic, the pulse being 88 and regular. The anteroposterior diameter of the chest appeared greater than normal and breath sounds were generally diminished. The edge of the liver was palpable and sharp three fingerbreadths below the right costal margin. No spider angiomas were noted.

Urinalysis showed albumin, grade 2. The hemoglobin measured 15.4 gm. per 100 cc., the erythrocytes numbered 5,380,000 and the leukocytes, 7100 per cubic millimeter of blood. The sedimentation rate was 15 mm. in 1 hour by the Westergren method. The urea measured 28 mg. per 100 cc. of whole blood. The serum bilirubin was nega-

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tive direct and 0.25 mg. indirect. The Kline flocculation test for syphilis was nonreactive. A bromsulphalein test for function of the liver showed 8 per cent retention in 1 hour. A roentgenogram of the thorax showed evidence of a Ghon complex and decreased peripheral markings suggesting emphysema (fig. 1). Roentgenograms of the gallbladder, esophagus, stomach, duodenum and colon were without evidence of abnormality except for moderate diverticulosis of the colon. No evidence of abnormality was apparent on roentgenograms of the sinuses and the skull. Examination of the optic fundi revealed bilateral papilledema of 1½ to 2 diopters. Only mild hypertensive arteriolar changes were noted and there was no peripheral retinopathy. The visual fields were normal. The electrocardiogram showed large P waves in leads I and II as often seen in cases of emphysema (fig. 2).

The results of neurologic examination were objectively normal except for the papilledema. Tests of pulmonary function indicating the presence of severe emphysema are shown in the table. Bilateral carotid angiograms and a ventriculogram were interpreted as being normal.

The hematocrit reading was 56 per cent on one occasion and 60 per cent 4 days later. The volume of whole blood was 81 cc. per kilogram of body weight and the plasma volume was 33 cc. per kilogram. Clinically the hematologic picture appeared to be that of mild secondary relative polycythemia associated with chronic pulmonary insufficiency.

The patient stopped smoking, practiced breathing exercises regularly and noted remarkable relief of his dyspnea and chronic productive cough. Penicillin was administered for 6 days because of the somewhat purulent appearance of the sputum, and this more than likely contributed measurably to his improvement. This moderate degree of improvement has been maintained with temporary recurrence of symptoms during even mild acute respiratory infections.

Case 2: A 53-year-old highway construction worker registered on December 14, 1955, because of shortness of breath of 6 months' duration, insidious in onset and gradually progressive without orthopnea. He also had noted some substernal pressure on exertion with prompt subsidence on resting. He had cough but no hemoptysis.

Physical examination showed dyspnea from the exertion of undressing. Oral hygiene was poor. Maximal expansion of the thorax was only half an inch, with normal resonance but distant breath sounds and prolonged expiration. Inspiratory crackling rales were noted in the bases of both lungs. The liver, spleen and superficial lymph nodes were not enlarged. Bilateral pedal edema was moderately severe. Ophthalmoscopic examination showed moderate bilateral papilledema and venous engorgement. The results of neurologic examination were normal. The venous pressure in the right arm was 18 cm. of water.

Urinalysis showed slight microhematuria. The hemoglobin measured 13.5 gm. per 100 cc. Erythrocytes numbered 4,310,000 and leukocytes 5600 per cubic millimeter of blood. The sedimentation rate was 2 mm. in 1 hour by the Westergren method. Urea measured 16 mg. and sugar 94 mg. per 100 cc. of blood. The bilirubin was negative direct and 0.72 indirect. Further studies of the blood showed the following values: chlorides 99.4 mEq. and carbon dioxide combining power 26 mEq. per liter

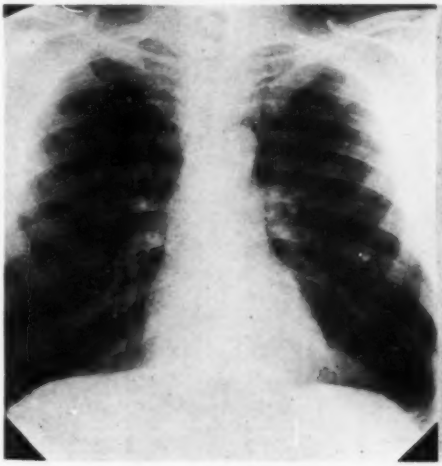

FIGURE 1

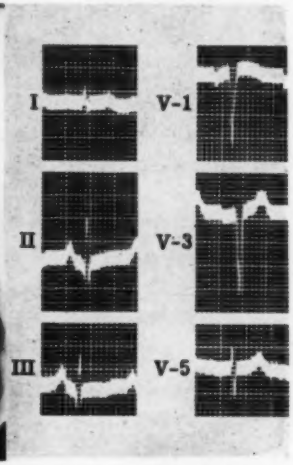

FIGURE 2

FIGURE 1: Posteroanterior view of the thorax (case 1). FIGURE 2: Electrocardiogram in case 1.

of plasma; albumin 3.49 gm. and globulin 1.6 gm. per 100 cc. of serum. No retention was present 1 hour after the bromsulphalein test for hepatic function. The Kline serologic test for syphilis was nonreactive. The hematocrit reading was 52 per cent on one occasion and 63 per cent 3 days later. An excretory urogram showed nephrolithiasis on the left. Results of studies of pulmonary function are shown in the table. Calcium measured 10.0 mg. per 100 cc. of serum and phosphate 4.2 mEq. per liter of serum. Similar values were found when these tests were repeated the next day. A roentgenogram of the thorax (fig. 3) showed evidence of advanced emphysema and considerable enlargement of the heart. The electrocardiogram showed evidence of right ventricular hypertrophy (fig. 4).

Treatment with digitoxin, aminophylline, mercaptomerin (thiomerin) and penicillin as well as isuprel aerosol resulted in diuresis so that the patient lost 25 pounds with clearing of the edema and considerable improvement in dyspnea. Phlebotomy of 500 cc. of blood was carried out on two occasions. Little change in the papilledema was observed during the 10 days of treatment. He was dismissed to go home, with advice to continue with treatment and to restrict his activities.

Case 3: A 38-year-old farm wife who had had asthma all her life registered in the Section of Ophthalmology because of progressive blurring of vision of several months' duration. She had been seen at the clinic on numerous previous occasions for chronic recurrent and protracted asthma as well as during several pregnancies. Acute papilledema was noted bilaterally and varied from 2 to 3+ diopters. Plotting of the visual fields showed an enlarged blind spot on the right resulting from the papilledema. The precise mapping of the left blind spot was inaccurate because of long-standing amblyopia which prevented adequate fixation. Eclampsia of pregnancy had led to fetal death in four of her seven deliveries. There had been no convulsions at other times.

On numerous examinations at the clinic her blood pressure was never greatly elevated, the highest reading being 144 mm. of mercury systolic and 96 mm. diastolic during her sixth pregnancy. Recent colds had been prolonged and associated with advanced dyspnea and wheezing (fig. 5). Activities had been almost eliminated during these respiratory infections.

Physical examination revealed dusky cyanosis of the face and fingernail beds and some impairment of sensorium. There were bilateral inspiratory rhonchi with depression of breath sounds especially on the left. The expiratory phase of respiration was longer than the inspiratory phase. She had bilateral varicose veins and pretibial edema of moderate degree. She weighed 134 pounds which was about 8 pounds more than her usual weight, and her height was 5 feet. The blood pressure measured 112 mm. of mercury systolic and 80 mm. diastolic, the pulse being 108 and regular. Neurologic examination gave essentially normal results.

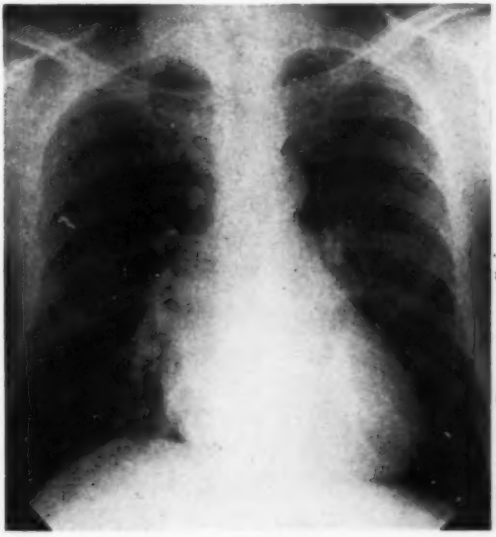

FIGURE 3

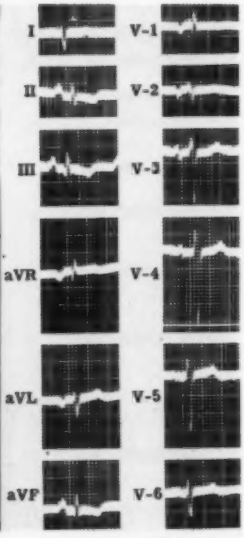

FIGURE 4

FIGURE 3: Posteroanterior view of the thorax (case 2) showing diffuse advanced emphysema and considerable cardiac enlargement. FIGURE 4: Electrocardiogram showing evidence of right ventricular hypertrophy (case 2).

RESULTS OF STUDIES OF PULMONARY FUNCTION

	Cases		
	1	2	3
Age (yr.) and sex of patient	52 M	53 M	38 F
Vital capacity (per cent of normal)	53	75*	62*
Total capacity (per cent of normal)	125	111	78
Residual volume/total capacity (per cent)	66	63	58
Maximal breathing	30	33	30
capacity (per cent of normal)		42*	43*
Expiratory slowing (grade 0 to 4)*	4†	4	4
Alveolar nitrogen (per cent)‡	14.2	5.5	10.5
Oxygen saturation			
At rest	92	90	79
Exercising	89	85	73
	(1 min.)	(5 min.)	(1.6 min.)
Breathing			
100 per cent oxygen	100	100	100

*After inhalation of 1 cc. of nebulized arterenol (1:400). †Trapping present.
‡Concentration of alveolar nitrogen after breathing 100% oxygen for 2 minutes.

Urinalysis showed a few leukocytes and erythrocytes microscopically, the specific gravity being 1.012. The hemoglobin measured 16.4 gm. per 100 cc. of blood; the erythrocytes numbered 5,000,000 and the leukocytes 6600 per cubic millimeter. The sedimentation rate was 3 mm. in 1 hour by the Westergren method. The hematocrit reading was 62 per cent. A blood smear did not show cellular immaturity. Roentgenograms of the thorax showed evidence of bilateral apical pleural thickening, adhesions at both costophrenic angles and fibrotic regions in the base of the left lung. A roentgenogram of the skull did not show any evidence of abnormality. The results of tests of pulmonary function are shown in the table.

Phlebotomy was performed three times and the hematocrit reading subsequently was found to be 55 per cent. When spinal fluid examination was done it was traumatic. The results of erythrocyte and leukocyte counts were not considered to be of

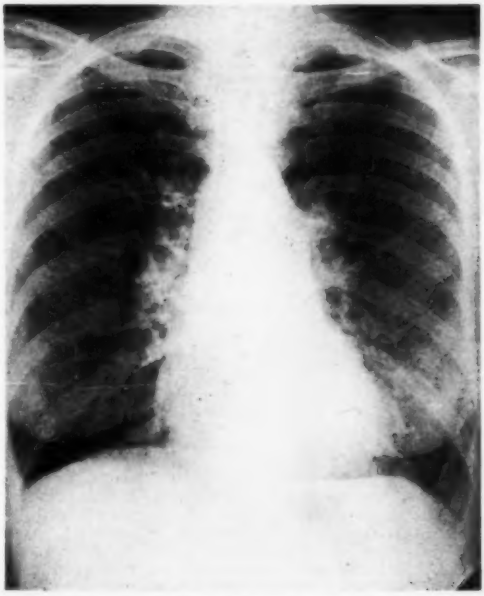

FIGURE 5: Posteroanterior view of the thorax (case 3) showing diffuse increase in pulmonary markings particularly in the bases which suggest the presence of bronchiectasis and fibrosis complicating long-standing asthma and emphysema.

diagnostic value. Spinal fluid protein measured 45 mg. per 100 cc. and the values for sugar and chlorides also were normal. A ventriculogram was normal.

A program of isuprel aerosol four times daily for 15 minutes was started and oxygen was used frequently while the patient was under observation. Periodic antibiotic therapy was advised for bronchial infection.

Only moderate improvement from the severe pulmonary insufficiency seemed to result and each respiratory infection was followed by a severer and longer attack. In February, 1957, the patient died, 2 years after her last examination at the clinic. Necropsy revealed chronic bronchitis and bronchiectasis, emphysema and advanced cerebral edema with generalized flattening of the convolutions, bilateral notching of the hippocampal gyrus and notching of the pes pedunculi on the left. The tonsils of the cerebellum were herniated and the brain stem was distorted. Cut sections did not show focal lesions.

Comment

Several factors apparently may contribute to papilledema occurring in patients with chronic pulmonary insufficiency. Polycythemia of the primary type[12] or secondary to pulmonary insufficiency with increased total blood volume may contribute to papilledema. Whether hypoxia alone or through stimulation of polycythemia contributes to papilledema is not certain. Austen and associates,[8] in reporting on four pulmonary cripples with neurologic abnormalities, three of whom had papilledema, commented that this funduscopic finding is not seen in patients with congenital cyanotic heart disease. We have not seen papilledema in patients with diffuse interstitial fibrosis characterized by hypoxemia but with no impairment of intrapulmonary mixing of gases. We have seen papilledema in two patients with the syndrome of obesity, hypoventilation and polycythemia. The physiologic abnormalities in these obese patients resemble those in our three cases reported herein. Thus retention of carbon dioxide seems to be an important factor in the genesis of papilledema.

Tests of pulmonary function showed rather advanced arterial hypoxemia in all three of our patients at rest and especially during exercise. In addition, however, relative polycythemia was demonstrated by the hematocrit reading or the hemoglobin determination or both. There was no clinical or laboratory evidence of polycythemia vera. Studies of lung volumes in the two men showed the characteristics of emphysema. The woman, who suffered repeated respiratory infections, had abnormalities characteristic of combined fibrosis and emphysema. These findings were supported by the small total lung capacity and by necropsy showing diffuse moderate bronchiectasis with peribronchial fibrosis.

Crucial features of pulmonary insufficiency associated with papilledema have been abnormally uneven intrapulmonary mixing of gases leading to retention of carbon dioxide and respiratory acidosis. Although frank alterations in carbon dioxide combining power were not always demonstrated at the time of the laboratory studies in our cases, grossly abnormal nitrogen washout patterns while the patients were breathing 100 per cent oxygen indicated that the stage was set for such complications. The frequent occurrence of hypoxia, polycythemia, signs of pulmonary hypertension and frank congestive failure further implicated retention of carbon dioxide as a causative factor since all of these abnormalities frequently coexist. Recent studies[13] showing large increase in cerebral blood flow with inhalation of high concentrations of carbon dioxide (5 to 7 per cent) lend support to the important role of high partial pressure of carbon dioxide in the blood in this syndrome. Furthermore, Simpson[3] and Davies and Mackinnon[4] demonstrated increased cerebrospinal fluid pressure as their subjects breathed gas mixtures containing high concentrations of carbon dioxide. Simpson[3] described herniation of the cerebellar tonsils into the foramen magnum found at necropsy in patients with pulmonary insufficiency and papilledema. Necropsy in the one fatal case in our series showed general cerebral edema as well.

Therapy with aerosol bronchodilators, appropriate antibiotics and mechanical assistors directed at improving ventilation with adequate elimination of carbon dioxide and oxygenation of the blood may bring about temporary and sometimes prolonged clinical improvement. The appearance of this syndrome, however, is usually an ominous sign prognostically.

SUMMARY

Papilledema in association with severe pulmonary insufficiency has been uncommon until recently when it has been reported with increased frequency. Common features of reported cases, including three from the Mayo Clinic, have included emphysematous pulmonary changes alone or associated with chronic asthma, bronchitis, or fibrosis. Impaired intrapulmonary mixing of gases has been of such severe degree as to lead to both hypoxia and retention of carbon dioxide. Frequently polycythemia, cor pulmonale and congestive failure also have been present. Neurologic manifestations have included altered sensorium, confusion, headache, weakness, blurred vision, muscular twitching and, occasionally, coma complicating respiratory infection, pharmacologic depression of respiration or therapy with high tensions of oxygen. Papilledema is apparently one of the most extreme and unusual signs of the adverse effects of severe pulmonary insufficiency on the central nervous system.

RESUMEN

El papiledema con insuficiencia pulmonar grave no ha sido común hasta recientemente, que ha sido relatado con frecuencia creciente.

Las características de los casos relatados, incluyendo tres de la Clínica Mayo, incluyen: trastornos pulmonares enfisematosos, solos o asociados con asma crónico, bronquitis o fibrosis. La mezcla de gases deficiente dentro del pulmón, ha sido tan severa que ha conducido a hipoxia y retención de bióxido de carbono.

También se encuentran frecuentemente policitemia, cor pulmonale y la insuficiencia congestiva. Las manifestaciones neurológicas han incluído trastornos sensoriales, confusión, cefalalgia, debilidad, visión borrosa, contracciones musculares y ocasionalmente coma complicando a una infección respiratoria, depresión formacológica de la respiración o con el tratamiento de oxígeno a alta presión. El papiledema es aparentemente uno de los mas extremos signos de los efectos adversos de la insuficiencia pulmonar grave sobre el sistema nervioso central.

RESUMÉ

L'oedème papillaire associé à une insuffisance pulmonaire grave avait été rare jusqu'à présent mais il est maintenant rapporté avec un fréquence accrue. Les traits communs des cas publiés, comprenant les trois de la Clinique Mayo, comportent des alterations emphysémateuses pulmonaires seules ou associées à de l'asthme chronique, de la bronchite ou de la fibrose. Le trouble du mélange intrapulmonaire des gaz a été d'une telle intensité qu'il a conduit à la fois à l'hypoxémie et à las rétention du gaz carbonique. Fréquemment, la polycythémie, le coeur pulmonaire et l'insuffisance cardiaque ont été notées également. Les manifestations neurologiques comprennent des troubles sensoriels de la confusion, des maux de tête, de l'asthme, une gêne de la vision, des crampes musculaires et occasionnellement le coma compliquant l'infection respiratoire, la dépression respiratoire due à certains agents pharmacodynamiques ou le traitement avec de l'oxygène à haute pression. L'oedème de la papille est apparemment l'un des signes les plus graves et les moins habituels des effets toxiques de l'insuffisance respiratoire sur le système nerveux central.

ZUSAMMENFASSUNG

Papillenoedem in Verbindung mit schwerer pulmonaler Insuffizienz galt bisher als ungewöhnlich, bis in letzter Zeit mit zunehmender Häufigkeit die Mitteilungen hierüber erschienen. Als gemeinsames Merkmal der mitgeteilten Fälle einschliesslich der drei aus der Mayo-Klinik Serie sich: emphysematöse Lungenveränderungen allein oder in Verbindung mit chronischem Asthma, Bronchitis oder Fibrose. Die Störung des intrapulmonalen Gasaustausches war von so schwerem Grad, dass sie sowohl zur Hypoxaemie, als auch zur Retension von CO_2führte. Öfter bestand auch eine Polycythämie, ein cor pulmonale und Herzversagen mit Stauung. Von neurologischen Manifestationen fanden sich eine Störung des Empfindungsvermögens, Verwirrtheit, Kopfschmerz, Schwächegefühl, Seostörungen, Muskelzucken und gelegentlich Koma als Komplikation einer Infektion des Respirationstraktes einer medikamentösen Herabsetzung der Atmung oder einer Therapie mit hochgespanntem O_2. Das Papillenoedem ist augenscheinlich eines der extremsten und ungewöhnlichsten Zeichen der ungünstigen Wirkungen schwerer pulmonaler Insuffizienz auf das Zentralnervensystem.

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Surgical Resection in the Treatment of Pulmonary Histoplasmosis: A Follow-up Study*

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Since Darling[1] in 1906 reported the first case of histoplasmosis and Watson and Riley[2] in 1926 found the disease in the United States, many outstanding contributions to the knowledge of the pathogenesis, epidemiology, pathology, and treatment of the disease, as well as to the study of the mycologic characteristics of Histoplasma capsulatum, have been made in this country and abroad.

Many recent publications have dealt with surgical treatment of "proved" pulmonary histoplasmosis. This paper reports a postoperative follow-up of surgical resections for this disease performed at the Mayo Clinic between March 1948 and December 1957.

Records of nine surgical cases of culturally proved pulmonary histoplasmosis have been found in the files of the clinic for that period, and form the basis for this report. Several other surgical cases have not been included in this study because cultural confirmation was lacking, even though microorganisms morphologically resembling Histoplasma capsulatum had been seen in specially stained sections of the resected tissues. Despite the strong likelihood that these cases also were instances of histoplasmosis, it was decided to consider them as inconclusive in view of recent reports,[3-6] and to eliminate them from the study, at the risk of being accused of "over-zealous conservatism."[7]

In the nine retained cases, six patients were males and three were females. The ages at the time of operation ranged from 27 to 56 years, averaging 39.3 years. The lesions in six cases were in the right lung, and their distribution included all major parts of it; but the three in the left lung were all in the upper lobe (table).

In only two cases was the diagnosis of histoplasmosis made preoperatively on the basis of a positive culture of the sputum for Histoplasma capsulatum. Cultures of the sputum, bronchial secretions, or gastric washings taken preoperatively were positive for Histoplasma capsulatum in four other cases, but were reported as such after the operation had been performed. In the remaining three cases, the etiology was proved only by culture of the operative specimen.

Seven of the nine cases had symptoms referable to the respiratory tract; the remaining two were discovered by evidence of a pulmonary lesion on a routine chest roentgenogram. Six patients had productive cough, and five of these had varying degrees of hemoptysis. Practically all the symptomatic patients complained of fever, asthenia, anorexia, and loss of weight.

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The laboratory data were not generally remarkable except for a moderate elevation of the erythrocyte sedimentation rate in two cases. Roentgenograms of the chest revealed cavitation of the lesions in four cases. This high incidence of cavitation in lesions produced by Histoplasma capsulatum is surprising, since it formerly was thought to be a rather uncommon finding.[12] Further significance was added by discovery of cavitation on gross examination of the surgical specimen in a fifth case, in which the cavity had not been identified roentgenographically. The roentgenologist did not report calcification in any lesion among the nine cases.

The histoplasmin skin test was strongly positive in five cases, slightly positive in one, doubtful in one, and negative in one; in the remaining case it was not given. The tuberculin reaction was negative in four cases and positive in four, and was not tested in the remaining case.

Lobectomy was employed in six of the nine cases, segmental resection in one, and local excision of the granuloma in two. No postoperative complications of significance were observed. Cultures of the operative specimen were positive for Histoplasma capsulatum in eight cases. In the other (case 9), four sputum cultures had been positive for Histoplasma and amphotericin B had been administered during several weeks before operation. Presumably this circumstance could account for the negative finding in the culture from the resected specimen.

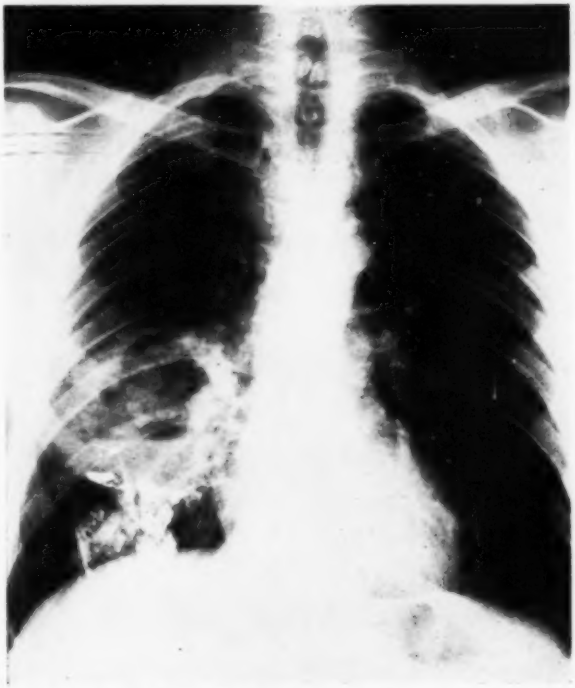

FIGURE 1 (case 1): View of lesion in 36-year-old male patient with 3-month history of malaise, slight fever, productive cough, and hemoptysis.

TABLE — DATA FROM NINE CULTURALLY PROVED CASES OF PULMONARY HISTOPLASMOSIS TREATED BY RESECTION

Case	Age, sex	Symptoms, preoperative	Lesion Place*	Lesion Kind	Positive cultures	Histoplasmin	Operation	Follow-up, yr.-mo.
1†	36,M	Yes	R-LL	Chronic cavitating lesion (fig. 1, 2)	Sputum, specimen (fig. 3)	Doubtful	Lobectomy	10-4
2†	34,F	Yes	R-UL	Chronic granuloma with cavitation	Sputum, specimen	++	Lobectomy	9-3
3	27,F	No	L-UL	Granuloma with cavitation	Specimen	+++	Segmental resection	7-2
4‡	42,M	Yes	L-UL	Caseating and cavitating granuloma	Sputum, specimen	Neg.	Lobectomy	0-8
5	40,F	Yes	R-ML, R-LL	Granuloma with slight caseation	Bronchial secretions, specimen	++++	Lobectomy	4-6
6	44,M	Yes	L-UL	Caseous granuloma with involvement of the nodes	Gastric washing, specimen	+++	Lobectomy	4-2
7	56,M	No	R-LL	Granulomatous pneumonitis in a discrete focus	Specimen	++++	Local excision	2-8
8	39,M	Yes	R-LL, R-hilum	Caseous granuloma	Specimen	Not done	Local excision	2-5
9	36,M	Yes	R-UL	Multiple nodules of caseous granuloma with multiple small cavities	Sputum	+++	Lobectomy	1-8

*R=right. L=left. UL= upper lobe. ML=middle lobe. LL=lower lobe.
†Previously reported by Hodgson and associates[10,11].
‡Has not answered the questionnaire.

A follow-up questionnaire was mailed to each of the nine patients, and to date all but one have submitted the information requested. The shortest follow-up period among the group of respondents was 1 year and 8 months, and the longest was 10 years and 4 months; the average was 5 years and 3 months. All eight currently were asymptomatic from the respiratory standpoint and were carrying out their normal everyday activities without limitations. Recent thoracic roentgenograms of these eight patients have shown no evidence of recurrence of their pulmonary disease. The histoplasma skin test, given 1 year postoperatively in one case and 3 years postoperatively in another, was positive in both.

The latest information on the patient who did not answer was derived from a postoperative recheck at the clinic 8 months after surgery. He then was complaining of a chronic cough; but a roentgenogram of his chest showed no evidence of recurrence, and sputum cultures were negative for Histoplasma capsulatum. Use of the date of this recheck makes the average follow-up period for the entire series 4 years and 9 months.

Comment

In the past few years, several publications have pointed out the possibility of atypical forms of Histoplasma capsulatum that resemble other fungi and Leishmania organisms.[6,12] On the other hand, it is known that small forms of Blastomyces dermatitidis may closely resemble Histoplasma in tissue sections and that dual infections by these two fungi may occur. Therefore the morphologic demonstration of the causative organism by means of specially stained histologic sections, although highly desirable and probably reliable in most cases, should be supplemented with adequate cultures whenever possible. As Weed[9] has pointed out, the process for culture of Blastomyces and Histoplasma from tissue removed at operation is so easy that it does not seem justifiable to jeopardize the patient's future by relying entirely upon histopathologic interpretation.

Recently Schwarz and Baum,[2] Tuttle and co-workers,[7] Layton and associates,[5] Tompkins and Schleifstein,[4] and Schwarz[6] have stressed the desirability of isolating the fungus from the patient before accepting the case as conclusively proved. This has been the main criterion for the seelction of cases for this report. However, further advances in histopathologic technics undoubtedly will make possible the inclusion of other cases not heretofore accepted as proved cases of histoplasmosis. The results

FIGURE 2 (case 1): Excised right lower pulmonary lobe, with large caseating lesion and cavitation.

Segal and co-workers[14] have obtained by use of this newer approach have been particularly rewarding in this respect.

Our results are in agreement with those reported by other authors; and in view of these results, we believe that surgical excision is definitely indicated in the treatment of the chronic granulomatous pulmonary lesions of histoplasmosis.

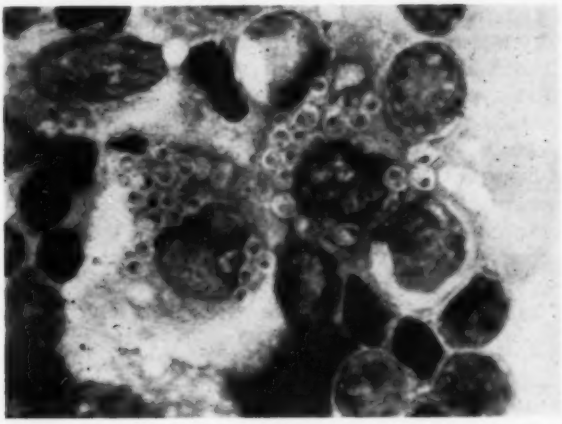

FIGURE 3 (case 1): Preparation of lesion, showing numerous intracellular forms of Histoplasma capsulatum (hematoxylin and eosin; reduced from x1500).

SUMMARY

Numerous recent reports have pointed out the good results usually obtained by resection of the chronic pulmonary lesions of histoplasmosis. A fairly long-term follow-up study of culturally proved cases seemed desirable at this time in order to ascertain the benefits of the treatment and to exclude the possibility of late recurrences.

The follow-up period in this series ranged from 8 months to 10 years and 4 months. All eight patients from whom current information could be obtained were in good health and free of evidence of recurrence. The remaining patient was doing well when last seen at the clinic 8 months after operation.

[Figures 1, 2 and 3 reproduced with permission from Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: "Pulmonary Histoplasmosis: Review of Published Cases and Report of an Unusual Case," *J. Thoracic Surg.* 20:97-104 (July), 1950.]

RESUMEN

Hay numerosas comunicaciones que relatan los buenos resultados obtenidos por la resección de las lesiones pulmonares crónicas de histoplasmosis. A fin de comprobar los beneficios del tratamiento y excluir la posibilidad de recurrencias tardías, pareció deseable un estudio de seguimiento a largo plazo de los casos demostrados por los cultivos.

El período de seguimiento de esta serie fué de 8 meses a 10 años y 4 meses. Todas los enfermos, de ocho de quienes s obtuvo información al día, staban en buena salud y libres de manifestación recurrencial. El enfermo restante se encontraba bien la última vez que se observó en la clínica, 8 meses dspués de la operación.

RESUMÉ

De nombreuses communications récentes ont mis en évidence les bons résultats généralement obtenus par la résection des lésions pulmonaires chroniques d'histoplasmose. Une surveillance prolongée des cas dont le diagnostic avait été affirmé par la culture semble désirable pour affirmer les bons résultats du traitement et exclure la possibilité de rechutes tardives.

La période de surveillance du groupe étudié s'étage de 8 mois à 10 ans et 4 mois. Les huit malades pour lesquels on put obtenir des renseignements d'une façon régulière étaient en bonne santé et indemnes re rchutes. Le malade restant allait bien lorsqu'on le vit à la clinique pour la dernière fois huit mois après l'intervention.

ZUSAMMENFASSUNG

Zahlreiche Berichte aus jüngster Zeit heben die guten Resultate hervor, die sich für gewöhnlich durch die Resektion der chronischen Lungenherde bei der Histoplasmose erzielen lassen. Eine sich über ein leidlich lange Zeitspanne erstreckende Nachbeobachtung an kulturell gesicherten Fällen erschien im gegenwärtigen Augenblick

wünschenswert zwecks Bestätigung der Vorzüge der Behandlung und Ausschluss der Möglichkei von späten Ruckfällen.

Die Nachbeobachtungszeit unseres Materials Beitrag zwischen 8 Monaten und 10 Jahren und 4 Monaten. Alle 8 Kranken, von denen laufende Informationen zu erlangen waren, befanden sich bei guter Gesundheit und boten keine Anhaltspunkte für einen Rückfall. Der neunte Patient war wohlauf, als er 8 Monate nach der Operation zum letzten Mal in der Klinik war.

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The President's Page

DO YOU WANT YOUR SON TO GO TO MEDICAL SCHOOL?

There was a time when reasonably good grades in a good school and the advantages of a cultured home were sufficient qualifications for medical school. But, as many a physician-father has found out too late, that time is no more. Getting into a medical school has become an intensely competitive matter. What is worse, it has also become a very impersonal matter. A medical school which admitted 25 to 50 students twenty years ago may now have classes of a hundred each, and it may have to select from over a thousand applications. There are four major sources of information by which students may be selected: interviews, recommendations, aptitude tests and academic records. Manifestly it is impossible to properly interview a thousand applicants each year. Aptitude tests have certain deficiencies, experience has shown, and recommendations are very difficult to evaluate unless the persons writing them are known in some fashion to the admissions committee. This means that the essential consideration in admitting students to medical school is the record that such students have made in their first three years of college.

Hence, if you want your son to go to medical school, it is essential that everything possible is done to compile a good pre-medical record. This means that preparation must begin long before college does. In the first place, the student who matures early has an advantage over the student who is still an adolescent when he begin college; this is a matter of luck. One can, however, provide a background at home which will be mentally stimulating. However, the local high schools are of fundamental importance; if they are not first class, your son will inevitably flounder around the first year of college, and he can well flounder himself out of the opportunity of practicing medicine. Although he might do very well his third year, he will be competing with others who did their floundering before they came to college.

Curiosity, zest, speculativeness and culture are very useful qualities in a doctor, but they are not qualities notably developed in college alone. There is too much information to be mastered there; it is necessarily a grind. But, when one is building a college record, there is no time for them in pre-medical work either. Your son must at all times remember that he is in college to get grades, and other considerations are secondary. Indeed, unless he is immensely bright, they are irrelevant. And the way to get grades is to grind.

For instance, a course in Shakespeare or Philosophy might be fun — it might be more than fun, it might be intensely iluuminating. But it is not for the pre-medical student. It is too much of an unknown quantity. He might get a C in it, and a C in Shakespeare or Philosophy might mean the difference between being a doctor and not being a doctor. The best way to get grades in college is to stick as closely as possible to those areas in which one's capacities have already been proved. When one must take courses in other areas, it is no trick at all to find courses, not so interesting as Shakespear perhaps, in which any student of moderate diligence can get good grades.

The same pragmatic concern for grades must determine his approach to his courses. In the first place, of course, he should memorize the information he is given, so far as he is able. Beyond that, he should be alert to the kind of emphasis the instructor gives the information. His aim should be to reproduce, as nearly as he can, the mind of his instructor on examinations. If the instructor has some eccentric enthusiasm, the boy can do very well for himself by adopting it for the time being. On the other hand, he should not get particularly interested in one phase of some subject matter; such interest would pull him away from other things upon which he will also be graded. The relationship between one course and another is of utterly no concern; no one will ask him questions about it. Above all he should avoid manifesting any pronounced individual trait which might antagonize an instructor. The instructor, being human, might give him a C for it.

This is, of course, a purposeful exaggeration. Medical educators everywhere are trying to make admission to medical school less mechanical and hence more perceptive. Some medical schools are concerned about the obvious limitations of a purely scientific education and are encouraging pre-medical students to look for breadth in education. We can expect a much improved situation within a few years. At the same time, admission to medical school is not going to become less competitive, and medical schools cannot and should not make any considerable allowance for the defects of a particular student's education. This means that the physician with a son aiming at medical school has a vested interest in the whole educational process, and not just his own alma mater. It will remain true, for example, that the dedication, or lack of it, of a teacher in the sixth grade can be decisive. This being the case, the quality of education in the sixth grade is the physician's concern.

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